Examining the role of comorbidity in socio-economic inequalities in short-term mortality among colon cancer patients in England

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Declaration of authorship

I, Helen Fowler, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Use of published work

This is a research paper style thesis. Two papers have been published during the period of PhD registration and are included within this thesis. A book chapter has been submitted for publication and is included in its submitted form. A further paper has been prepared for submission and is included in its form for submission. Helen Fowler was the lead and corresponding author on all included papers and the book chapter. She planned and carried out the literature reviews, conducted the data analysis and prepared all drafts of each paper and the book chapter. The co-authors worked with Helen to plan the content of each, provided input and feedback on the data analysis and provided comments on the drafts prepared by her.

Abstract

Colon cancer is one of the most common cancers diagnosed in England. Despite the universal healthcare system, the most deprived groups of colon cancer patients have a poorer prognosis than the more affluent patients, particularly in the short-term following diagnosis.

Comorbidity is considered to be a prognostic factor in cancer outcomes. Moreover, the presence of comorbidity tends to be associated with increased levels of socio-economic deprivation. In this thesis I investigated the role that comorbidity plays in socio-economic inequalities in ninety-day mortality after diagnosis with colon cancer. My research used population-based England national cancer registry data linked with Hospital Episode Statistics (HES), National Bowel Cancer Audit (NBOCA) and Route to Diagnosis data of approximately 100,000 patients diagnosed with colon cancer between 2009 and 2013.

This research emphasised the increased burden of comorbidity and multiple comorbidity among the most deprived cancer patients. The presence of comorbidity influenced the short-term mortality of the most deprived patients following diagnosis with colon cancer, but stage of diagnosis and the receipt of surgical treatment appeared to be influential factors in socio-economic inequalities in short-term mortality. Accounting for time-varying proxy measures of comorbidity severity reduced some of the differences in ninety-day mortality between the most and least deprived patients with pre-existing diabetes, COPD and cardio-vascular conditions, but disparities in mortality still remained, suggesting other factors may be contributing towards inequalities between these groups of patients.

The growing prevalence of multimorbidity and the comorbidity burden among cancer patients highlights a need for healthcare systems equipped and resourced for managing multiple chronic conditions simultaneously. Further investigation into healthcare utilisation and access to optimal care may provide insights into opportunities to improve outcomes of deprived patients living with chronic diseases who go on to develop cancer. Mechanisms to be explored include the interplay between deprivation, chronic disease burden, stage at cancer diagnosis and cancer treatment options.

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Contents

List of abbreviations

AIDS – Acquired Immune Deficiency Syndrome

CCI – Charlson Comorbidity Index

CHF – Congestive Heart Failure

COPD – Chronic Obstructive Pulmonary Disease

CVD – Cerebrovascular Disease

HES – Hospital Episode Statistics

HIV – Human Immunodeficiency Virus

ICD – International Classification of Disease

ICU – Intensive Care Unit

LSHTM – London School of Hygiene and Tropical Medicine

MAR – Missing at Random

MI – Myocardial Infarction

NBOCA – National Bowel Cancer Audit

NHS – National Health Service

OPCS-4 – Office of Population Censuses and Surveys Classification of Interventions and Procedures (fourth version)

PHE – Public Health England

PVD – Peripheral Vascular Disease

SES, SEP – Socio-economic status, Socio-economic position

SMCFCS – Substantive Model Compatible Fully Conditional Specification

TNM – Tumour Nodes Metastases

UK – United Kingdom

WCE – Weighted Cumulative Exposure

List of tables and figures

Chapter 1 - Background

The prevalence of chronic disease is increasing,[1] as is the prevalence of people living with multiple chronic conditions, or multimorbidity.[2-4] Non-communicable chronic diseases are responsible for considerable mortality and morbidity and thus represent an important public health issue.[5] Among them, cancer is the second most common cause of death in the world after cardio-vascular diseases, and accounted for approximately 9.6 million deaths globally in 2018.[6]

Colon cancer is one of the most commonly diagnosed cancers: approximately 8% of all cancers diagnosed in England in 2017 were cancers of the colon.[7] Differences between socio-economic groups in terms of colon cancer prognosis are evident in England, with the most socio-economically deprived groups of patients having a poorer prognosis than the less deprived patients.[8, 9] These inequalities have persisted despite government initiatives, such as the NHS Cancer Plan in England, that were designed to reduce them.[10, 11] Moreover, socio-economic inequalities in colon cancer prognosis appear to be most apparent in the short-term following diagnosis.[12]

Cancer patients living with additional chronic diseases, or comorbidities, may have poorer prognosis than those without,[13] while the burden of living with multiple chronic diseases tends to be greater among the most deprived.[14, 15] There is a lack of information in the scientific literature on the role of comorbidity in socio-economic inequalities in short-term cancer outcomes. More clarity in this will be informative for healthcare strategy and clinical guidelines to manage multiple chronic diseases simultaneously and to improve outcomes among more deprived groups of cancer patients.

Aetiology and epidemiology of colon cancer

Aetiology

The colon, or large intestine, is made up of four parts - the ascending colon, the transverse colon, the descending colon and the sigmoid colon - and extends from the cecum to the rectum.[16] It is the final part of the digestive system, and its function is to reabsorb fluids and to process waste products and prepare for their elimination from the body.[16] Waste matter passes from the colon to the rectum for transportation or storage.[17]

Approximately two-thirds of colorectal cancers originate in the colon.[18, 19] Colon cancers and rectal cancers share similar aetiology. The majority of cases of colorectal cancer are sporadic,[20] that is, they occur in people without a family history of colorectal cancer or an inherited change in their DNA that would increase their risk for developing this cancer.[21] Non-hereditary risk factors for colorectal cancer include lifestyle factors and non-modifiable risk factors such as age and sex. Modifiable or lifestyle risk factors are responsible for up to 50% of the risk of colorectal cancer,[18] and may include increased body weight[22] and physical activity[23, 24] or dietary factors such as increased consumption of red meat,[18, 25, 26] lower dietary fibre intake[27] and excessive alcohol consumption.[18, 28] There is evidence to suggest that tobacco smoking also increases the risk of developing colorectal cancer.[22, 29, 30] Certain health conditions have been associated with an increased risk of developing colorectal cancer, such as Diabetes Mellitus.[31] Inflammatory conditions, such as Crohn's disease or ulcerative colitis, also carry some risk, but these conditions only account for 1-2 percent of all cases of colorectal cancers in the general population.[20]

It is estimated that 10-30% of cases of colorectal cancer have a familial aetiology, in other words they occur in people who have biological relatives with a history of colorectal cancer or colorectal adenoma.[18, 20] An additional 5% of colorectal cancers arise from inherited cancer susceptibility syndromes resulting from mutations in DNA, such as Lynch syndrome or Familial Adenomatous Polypous.[18]

Incidence

The incidence rate of colon cancer has historically been higher in developed countries than in less developed countries.[25] This may be linked with dietary patterns, given the prominence of the western diet (i.e. a diet with a high intake of fats and animal-source foods, refined carbohydrates and added sugars[32]) in many developed nations, and the association between this style of diet and incidence of colorectal cancer.[33] The incidence of colon cancer typically increases with age,[34] although recent evidence suggests colon cancer incidence has been increasing among younger people in England[35] as well as in the United States[36] and Europe.[37] Incidence patterns according to age indicate that men may develop colorectal cancer earlier in their life than women.[38]

The evidence regarding an association between colon (or colorectal) cancer incidence and socio-economic position appears to be mixed. Some studies have reported measures of a lower socio-economic position, for example income, education and occupation, as risk factors for colorectal cancers,[39-42] while another reported the risk as being higher in affluent populations.[43] The association between incidence and socio-economic position may be stronger in men, in comparison with women.[39, 40, 43]

Prognosis

Colorectal cancers are the fourth most common type of cancer diagnosed in England.[44] One-year net survival (i.e. survival from cancer after accounting for death from other causes) among colon cancer patients is poorer than that among patients with other common cancers, such as cancer of the rectum. Among patients diagnosed with colon cancer in England, one-year age-standardised net survival from colon cancer was reported as approximately 75% in women and 77% in men, while it was approximately 82% from rectal cancer among both sexes.[45] One-year net survival from colon cancer in England has been persistently poorer than in several comparable developed countries. For example, between 2005-2009, age-standardised one-year net survival was approximately 74% in England while in Canada, Sweden and Australia it ranged between 81% and 84% [46]

Socio-economic inequalities and prognostic factors

Patient characteristics, tumour characteristics and healthcare factors can all influence prognosis following colon cancer diagnosis. For example, factors such as patient age and tumour stage at diagnosis[47] or comorbidity[48] have been shown to be associated with one-year net survival from colon cancer. Socio-economic inequalities are found throughout the cancer continuum, from pre-diagnosis to receipt of palliative care.[49] These inequalities are evident in colon cancer outcomes, and have been reported from 30-days following diagnosis[12] up to one-year[10, 11, 50] and beyond.[12, 51-53]

Many of the studies investigating colon or colorectal cancer prognosis have focused exclusively on post-operative patients. Factors associated with thirty-day post-operative mortality following surgery include age,[54] presence of comorbidity,[55, 56] stage and operative urgency.[57] A population-based study of colorectal cancer patients in England reported that the most deprived groups of patients had 32% increased odds of thirty-day post-operative mortality, even after adjusting for factors thought to differ between socio-economic groups, such as stage, comorbidity and emergency presentation.[57] Age,[58] stage, and mode of surgery continued to be prognostic factors in mortality up to one year following surgery.[54, 59]

Multimorbidity

The terms multimorbidity and comorbidity are widely, and often interchangeably, used in the scientific literature when discussing the prevalence of chronic health conditions or diseases. To distinguish between the two, multimorbidity is a general term that implies the existence of two or more diseases or conditions,[60] while the term comorbidity describes the existence of a long-term health condition in the presence of a primary disease of interest.[61]

Risk factors for multimorbidity have not been widely researched.[62] Multimorbidity within the general population tends to be most prevalent among older age groups, but there is also an association with socio-economic position.[14, 15, 63] A study of 1.75 million patients in Scotland reported that onset of multimorbidity occurred 10-15 years earlier among people living in the most deprived areas, compared with those in the least deprived areas.[64] Lifestyle factors such as tobacco smoking, dietary factors (such as lower intake of fruit, vegetables and whole grain foods), body mass index (BMI) and physical inactivity are potential risk factors for multimorbidity.[65-68]

While the prevalence of multimorbidity is increasing,[2-4] the management of these patients may be challenging within the confines of healthcare systems and guidelines that appear to be single disease focused.[62, 64, 69] Therefore, the investigation of outcomes of patients with multiple chronic conditions is a pertinent topic for cancer research.

Aims and objectives

Aims

The overarching aim of this thesis is to investigate patterns in comorbidity in cancer patient populations, and to examine the role of comorbidity in the socio-economic inequalities in short-term mortality among colon cancer patients

Objectives

1. Examine the influence of prognostic factors on socio-economic differences in ninety-day mortality among colon cancer patients
2. Describe and evaluate the measurement of comorbidity prevalence in cancer patient populations, by deprivation
3. Investigate the role of factors that could indicate severity of comorbid conditions, such as time with comorbidity and timing and duration of hospital visits since comorbidity diagnosis, on socio-economic inequalities in ninety-day mortality among colon cancer patients

Population-based data used in this research

The research conducted for this thesis used population-based National Cancer Registry data of up to 102,216 patients diagnosed with colon cancer in England between the years of 2009 and 2013.[70] These data were linked with electronic health records (Hospital Episode Statistics,[71] HES), Route to Diagnosis data and with cancer-site specific clinical data (National Bowel Cancer Audit,[72] NBOCA) compiled by clinicians working with patients in hospitals in multi-disciplinary teams. In addition, the research conducted for Chapter 4 of the thesis used the cancer registry data linked with HES records of patients diagnosed with cancer of the rectum (N = 56,342), lung (N=165,677) or with Hodgkin lymphoma (N= 7,420) in England between 2009 and 2013. Inclusion criteria were patients aged 15 years and over at cancer diagnosis, the diagnosis was of a primary or invasive tumour (i.e. the cancer originated at the respective cancer site or had spread into surrounding, healthy tissue), and there were at least six years of HES records prior to cancer diagnosis from which to obtain information on patient comorbidity.

The data linkages were undertaken by Cancer Survival Group colleagues. The registry data was linked with HES and with NBOCA at the patient level using a hierarchical algorithm initially developed by Shack et al.[73] and further developed internally. The algorithm was based upon availability of patient identifier variables (NHS number, postcode, date of birth and sex) and prioritised linkage of records according to the combination in which these patient identifier variables were available. Following this, tumour-level data were linked by patient variables, tumour site and diagnosis date.

The registry data represented more than 99% of cancer registrations in England.[70] Approximately 90% of these records linked with the HES records, while approximately 80% linked with NBOCA data. Route to Diagnosis information was linked with registry data using registry identifier and registry patient identifier variables present in both sources. Approximately 95% of registry records matched with known information on Route to Diagnosis.

National Cancer Registry data and Cancer Analysis System (CAS)

Patients diagnosed with cancer in England are registered with the National Cancer Registry, which collects data about the patients and about the characteristics of the cancer or tumour. The cancer registry data used in this research provided information on date of diagnosis, vital status, date of last follow up and cancer site (based upon the coding system of the tenth version of the International Statistical Classification of Diseases and Related Health Problems, ICD10[74]). Cancer of the colon was identified by the ICD10 code C18, while cancers of the rectum or lung or Hodgkin lymphoma were identified by the ICD10 codes C19-C20, C34 and C81, respectively. Patient information obtained from the registry data included age at diagnosis, sex and residential postcode at the time of cancer diagnosis. Cancer Analysis System is a national database that combines cancer registry data with data from other sources. These data provided information on pathological and clinical staging components and summary stage at diagnosis (based on the Union for International Cancer Control (UICC) TNM classification of malignant tumours[75]).

Hospital Episode Statistics (HES)

The HES data provided information on inpatient admissions (Admitted Patient Care) and outpatient appointments at National Health Service hospitals pre- and post-cancer diagnosis. These data were available for hospital admissions or appointments occurring between 1st January 2003 and 31st December 2013. Inpatient admissions records are defined in terms of 'episodes' – an episode is a term given to define a period of care in hospital under one consultant, and is represented by one observation in these data. Single admissions to hospital (or 'spells') can be made up of multiple episodes. The outpatient data capture same-day appointments with healthcare practitioners in hospitals.

These data were used to obtain information on comorbidities diagnosed up to six years pre-cancer diagnosis. This six-year lookback was based on previous research on the optimal lookback period required to capture information on comorbidity.[76] The diagnostic fields within inpatient records and outpatient records contained ICD10 codes, which provided information on the condition(s) the patients had. Hospital episode start and end date variables in the inpatient records, and appointment date variables in the outpatient records, were used to derive information on the (minimum) time with the comorbid condition. Episode date variables (and a variable defining the order in which multiple episodes occurred) were used to derive the frequency and duration of hospital admissions since the condition was first recorded in HES.

Information on the type of surgical procedure received was available in the inpatient and outpatient data, and was based upon the coding of the Classification of Interventions and Procedures, fourth version - OPCS-4.[77] These data also provided information on the date a surgery occurred, and whether it was performed as an emergency or an elective procedure.

National Bowel Cancer Audit data (NBOCA)

The NBOCA data are clinical data compiled by clinicians and other healthcare professionals working with colorectal cancer patients in hospitals as part of multi-disciplinary teams. These data were used to obtain information on the primary surgical treatment that the patient received (according to OPCS-4 codes), the date of the surgery, and stage at diagnosis (obtained using the available information on TNM pathological and clinical staging components and summary stage). This information was used in the research conducted in Chapter 3 of this thesis.

Route to Diagnosis

This is derived from an algorithm that uses information on patient pathways from HES, cancer registry data and other cancer-specific data sources (Cancer Waiting Times and cancer screening data) to categorise every case of cancer registered in England into one of eight Routes to Diagnosis.[78] Routes include GP referrals, screening and emergency presentation. This variable was used to identify patients who had been diagnosed with colon cancer via emergency presentation.

Income Deprivation domain of the Indices of Multiple Deprivation (IMD)

The measure of socio-economic deprivation used in the research conducted for this thesis was the Income deprivation domain of the Indices of Multiple Deprivation (IMD).[79] This is an ecological measure of deprivation, and represents the proportion of the population at the Lower layer Super Output Area (LSOA) (mean population 1,500) level experiencing deprivation due to low income.

The Income Deprivation domain score represents the number of individuals with income deprivation within an LSOA as a proportion of all individuals within that LSOA. The number of income deprived individuals is calculated by summing the following five indicators:[80]

i) Adults and children in Income Support families

ii) Adults and children in Income-Based Jobseeker's Allowance families

iii) Adults and children in Pension Credit (Guarantee) families

iv) Adults and children in lower income Child Tax Credit families (income below 60% of the median), and

v) Asylum seekers in receipt of subsistence or accommodation support

The domain score is used to rank all LSOAs from most to least deprived, and the order of these rankings determines the grouping of LSOAs into deprivation quintiles. My research used the quintiles of the Income Deprivation domain. Residential postcode at the time of cancer diagnosis was used to determine a patient's LSOA and thus their deprivation quintile.

Development of algorithms

During the course of the research conducted for this thesis, I worked on the development of algorithms to obtain robust information on key variables of interest from these data sources.

Stage at diagnosis

The CAS and clinical audit (NBOCA) data both provided information on stage at diagnosis. I assisted in the development of a hierarchical algorithm to derive the most robust definition of stage using information from both data sources, to manage discrepancies between the two sources, and to manage the scenario in which information is missing in one but not both sources. The algorithm provides a single stage category for each tumour based on a prioritisation of information according to data source and the various individual components of tumour stage. It follows a restrictive or non-restrictive approach to summarising stage, according to the availability of information for each of the tumour (T), lymph nodes (N) and distant metastases (M) components, and is based upon the rules of the UICC TNM classification system.[75] I was a co-author of a paper published in the British Journal of Cancer in 2016 detailing the methodology behind this algorithm.[81]

In deriving the stage at diagnosis variable, the clinical audit data (NBOCA) were the preferred data source of T, N and M staging component information, while CAS supplemented missing NBOCA data. Within the NBOCA data it was possible to have multiple records for a single tumour, and thus potentially differing information on the T,N and M components. To address this, the algorithm prioritised the staging information on the date closest to the date of cancer diagnosis. In the rare event that there were multiple records for that tumour on that particular date, the record with the lowest values of individual T, N and M components was given priority, in line with general TNM classification rules.[75]

The following step of the algorithm was to select the individual T, N and M components from pathological, clinical or unknown (integrated) sources of information. The pathological information was prioritised over the clinical information for T and N because microscopic evidence was assumed to better determine tumour extent and nodal involvement than clinical sources.[82] For M, clinical information was given priority over pathological information.[82] Lastly, clinical or pathological data was prioritised over T, N or M information from an unknown source.

The final part of the algorithm was to apply the TNM definitions[75] for grouping of stage to obtain a summary TNM stage variable. The algorithm considers the values of M, N and then T to summarise stage into one of four classifications – from stage 1 (local) to stage 4 (metastatic). The summary stage variable used in the analyses conducted for this thesis had been derived using a restrictive approach – i.e. only considering observations of tumour stage in which valid information was available for all individual TNM components. The process followed by the algorithm to derive grouped TNM stage via the restrictive approach is illustrated in Appendix Figure 1.

Comorbidity

I assisted in the development of an algorithm to extract information on 17 of the conditions of the Charlson Comorbidity Index[83] (Table 1.1) plus obesity, using information in the diagnostic fields of HES records. Each of the conditions was defined according to the grouping of ICD10 codes for that condition proposed by Quan et al.[84] The algorithm generated binary variables for each condition for each six-month time interval up to ten years prior to cancer diagnosis, to indicate if it had been recorded during any hospital admissions occurring during that interval. Using these binary variables, it was then possible to summarise the comorbidities present during any given timeframe up to ten years prior to cancer diagnosis. I was a co-author on a paper describing the methodology behind this algorithm, which was published in PLoS One in 2017.[76]

Table 1-1 The seventeen conditions of the Charlson Comorbidity Index included in the algorithm

Conditions	
Myocardial infarction	Congestive Heart Failure
Peripheral Vascular Disease	Cerebrovascular Disease
Dementia	Chronic Obstructive Pulmonary Disease
Rheumatic Disease	Peptic ulcer disease
Mild liver disease	Diabetes without chronic complications
Diabetes with chronic complications	Hemiplegia or paraplegia
Renal disease	Moderate or severe liver disease
AIDS/HIV	Any malignancy
Metastatic solid tumours	

Receipt of major surgery

Information on surgical treatment received was available from both the NBOCA and HES data. I developed an algorithm to extract information on the first major surgery received in the time window from 30 days prior to 90 days following cancer diagnosis. Major surgery was considered to be surgery with curative intent, and was categorised as such according to definitions agreed by National Cancer Intelligence Network Site Specific Clinical Reference Groups.[85] The algorithm also defined whether the surgery was received as an elective procedure, or following emergency presentation, using information on admissions in the HES data.

Chapter 2 - Comorbidity and cancer

The presence of additional chronic conditions can be influential at several points on the cancer patient pathway, from the time leading up to the diagnosis of cancer to ultimate cancer prognosis. Additionally, there is some evidence suggesting that these comorbidities may explain some of the social or socio-economic disparities in cancer prognosis. This is discussed in more detail in the following manuscript, "The role of comorbidities in the social gradient in cancer survival in Europe", a chapter I drafted for a book entitled "*Social environment and cancer in Europe: towards an evidence-based public health policy*" to be published by Springer.

The research conducted for writing this book chapter involved reviewing the published scientific literature on studies investigating comorbidity as an explanatory factor in social or socio-economic inequalities in survival or mortality from any type of cancer. The literature search was undertaken using Medline, EMBASE and Pubmed databases using the keywords in Table 2.1 for articles published between January 1990 and November 2019. The review was restricted to articles written in English.

Table 2-1: Topic and search terms for literature review

Topic	**Search terms**
Primary disease	cancer OR malig*
Comorbidity	comorbid* OR multimorbid*
Social position	socio* OR social OR income OR educ* OR occupation*
Social gradient	Inequal* OR inequit* OR gradient
Survival	Survival OR mortality OR prognosis

The book chapter firstly examines the role of comorbidity as a prognostic factor in cancer outcomes, considering how it may influence stage at cancer diagnosis and the management of cancer following diagnosis. It then reports and summarises the findings of the published scientific studies from European countries examining the role of comorbidity in inequalities in cancer survival.

The chapter is included in this thesis in its entirety and in manuscript format, as submitted to the book editors.

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SECTION A – Student Details

Student	Helen Fowler
Principal Supervisor	Bernard Rachet
Thesis Title	The role of comorbidity in socioeconomic inequalities in short-term mortality among colon cancer patients in England

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	As a chapter of a book published by Springer entitled: "Social environment and cancer in Europe: towards an evidence-based public health policy"
Please list the paper's authors in the intended authorship order:	Helen Fowler, Pamela Minicozzi, Miguel Angel Luque-Fernandez, Bernard Rachet
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of the book chapter. I devised the structure of the chapter, conducted the literature review, and prepared the draft of the chapter. The co-authors provided comments on the chapter draft.

Student Signature: [redacted] **Date:** 16/10/20

Supervisor Signature:  **Date:** 19 October 2020

The role of comorbidities in the social gradient in cancer survival in Europe

Helen Fowler, Pamela Minicozzi, Miguel Angel Luque-Fernandez and Bernard Rachet

Social disparities in cancer survival in Europe are evident, as discussed in earlier chapters of this book. Survival is commonly worse among the more socio-economically deprived cancer patients, an issue that is pertinent for many different cancer types. The prognosis of cancer patients can be affected by the presence of additional diseases or comorbidities, with the more deprived patients tending to experience a higher prevalence of comorbid conditions. This chapter aims to examine the role played by comorbidities on the social gradient in cancer survival that is often observed in Europe.

To illustrate the interconnections of comorbidity, and variables associated with comorbidity, with these social inequalities, the Directed Acyclic Graph (Fig. 22.1) depicts assumed causal relationships between social position and cancer survival. The chapter will discuss these relationships in turn, and will then summarise the findings of published scientific studies investigating comorbidity as an explanatory factor in social or socio-economic inequalities in cancer survival in European countries.

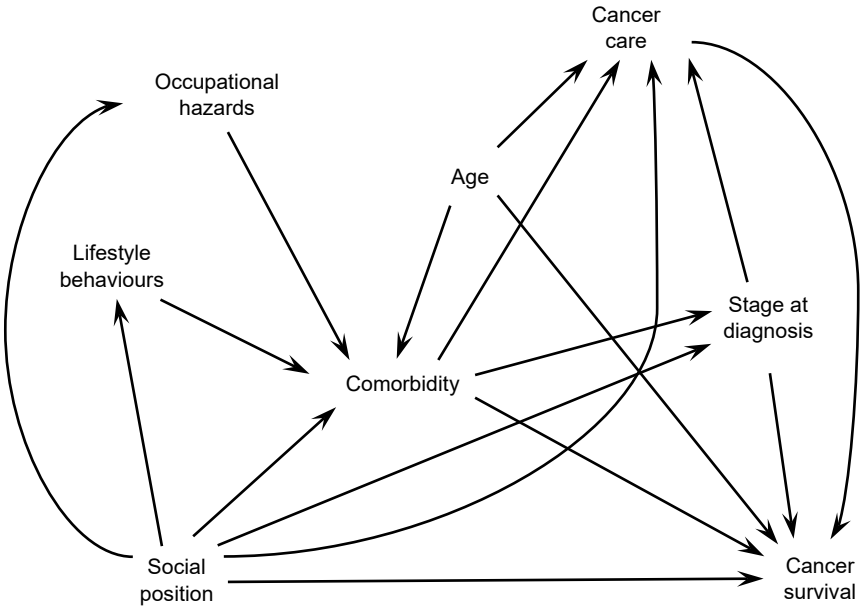

Fig. 22.1 Directed Acyclic Graph (DAG) illustrating the interconnections of comorbidity in the relationship between social position and survival from cancer

22.1 Defining comorbidity

The terms multimorbidity and comorbidity are frequently used in the literature when discussing disease prevalence. Multimorbidity is a broad term that refers to the presence of two or more chronic diseases, while comorbidity describes one or more other chronic diseases that co-exist with a primary disease of interest (Porta et al. 2014). Comorbidity is commonly considered as a prognostic factor in cancer outcomes (Sarfati et al. 2016). The distinction between multimorbidity, comorbidity and related terms is particularly timely with the ever-increasing number of studies examining the impact of multiple chronic conditions (Nicholson et al. 2019). Indeed, the Pubmed Medical Subject Headings (MeSH) were updated in January 2018 to include multimorbidity as a separate term from comorbidity.

Although there are a variety of approaches to quantifying comorbidity within the scientific literature, there is no agreed gold standard for measuring comorbidity in the presence of cancer (Sarfati 2012). The lack of consensus in the best approach to defining and measuring multiple chronic diseases challenges the ability to compare findings across populations and draw upon this for the development of guidelines and interventions (Johnston et al. 2019). Studies of comorbidity and cancer outcomes may define comorbidity in terms of specific chronic conditions (Bare et al. 2017) or consider the patient's full comorbidity burden based on a summary metric, such as the widely-used Charlson Comorbidity Index (CCI) (Charlson et al. 1987). Other metrics of comorbidity often used in the cancer patient setting include the Adult Comorbidity Evaluation – 27 (ACE-27) developed for adult cancer patients (Piccirillo et al. 2008), and the Elixhauser index (Elixhauser et al. 1998) or age-adjusted CCI (Charlson et al. 1994) which are not specific to cancer patients. Another variable in quantifying comorbidity relates to the time window during which the presence of comorbidities is considered relevant for defining the patient's comorbidity status once the cancer has been diagnosed. Studies have investigated the overall lookback time period for comorbidities and / or the length of the time that is excluded prior to primary disease diagnosis (Preen et al. 2006; Shack et al. 2010; Maringe et al. 2017), offering different perspectives on the most appropriate time period to use. It may not be possible to establish a universally agreed 'optimal' time window, given that this window may vary between studies, depending on the research question and underlying assumptions towards comorbidity. Another anomaly is whether summary metrics used for cancer comorbidity should consider previous malignancies as a comorbidity. Additionally, there are a variety of sources of patient-level information on cancer comorbidity ranging from information collected during cancer treatment clinical trials to routine, administrative sources such as primary or secondary care data. In

comparing data sources, the strengths and limitations of each can vary according to quality, reliability and generalisability (Geraci et al. 2005).

22.2. Social gradient in comorbidity prevalence

Comorbidity prevalence has been shown to be associated with socio-economic position, both in a general context (Macleod et al. 2004; McLean et al. 2014; Moffat and Mercer 2015) - i.e. not specific to a nominated primary disease - and within the context of cancer (van Leersum et al. 2013; Aarts et al. 2015; Fowler et al. 2020). For example, one study found mixed physical and mental health multimorbidity was more common among more deprived than less deprived people at all ages under 75 years (McLean et al. 2014). Furthermore, a low socio-economic position was observed to be associated with a higher risk of comorbidity, independently from the cancer under study (Louwman et al. 2010; Fowler et al. 2020).

Additionally, many cancers and comorbid conditions share common aetiological risk factors, which in turn are associated with increasing levels of socio-economic deprivation. For example, the development of common cancers such as lung or colorectal cancers has been linked to tobacco smoking (Schottenfeld and Fraumeni 2006; Tindle et al. 2018), dietary habits and alcohol use (Danaei et al. 2005; Haggar and Boushey 2009). Tobacco smoking is also linked to conditions such as chronic obstructive pulmonary disease (Devereux 2006; Buist et al. 2007; Laniado-Laborín 2009) and Type 2 diabetes (Hu et al. 2001; Wannamethee et al. 2001), and with socio-economic position (Cavelaars et al. 2000; Giskes et al. 2005; Huisman et al. 2005; Hiscock et al. 2012). Other risk factors such as poor dietary habits, lack of physical activity and obesity can also typically follow a social gradient (Alcaraz et al. 2020). The risk of excess alcohol consumption and binge drinking has been shown to be socio-economically patterned (Fone et al. 2013), while alcohol consumption and raised body mass index are both associated with liver disease, with evidence of a synergistic interaction between the two (Hart et al. 2010). Moreover, health conditions that are typically most prevalent among people of a lower socio-economic position, such as diabetes (Fano et al. 2013; Grundmann et al. 2014; Kim et al. 2015), can be associated with an increased risk of a wide range of cancers (Dankner et al. 2016).

22.2.1. Comorbidity prevalence among cancer patients in Europe

Within the epidemiological literature, studies investigating the role of comorbidity in cancer outcomes often summarise the overall comorbidity status of a patient. European studies providing detailed discussion of the prevalence of comorbid conditions among cancer patients are fairly limited in number, and the majority of the research has been conducted in the north rather than in the south of Europe. Several studies conducted in the Netherlands suggest that the prevalence of chronic disease has increased over time (Uijen and van de Lisdonk 2008; van Leersum et al. 2013; Aarts et al. 2015; van Oostrom et al. 2016). Moreover, the rise in chronic non-communicable diseases, including cancer, is likely to increase dramatically during the coming years in line with the changing demographic structure of the population due to the ageing phenomenon (Thun et al. 2010; World Health Organisation and US National Institute of Aging 2011). The annual number of new cancer cases worldwide is projected to rise to 17 million by 2020 and to reach 27 million by 2030 (Sutcliffe 2012). Although the population of Europe represents only one eighth of the total world population, currently one quarter of the global total of cancer cases are in Europe (World Health Organisation 2020).

Among the studies of cancer comorbidity in Europe, a study of small-cell lung cancer (SCLC) patients (Aarts et al. 2015) and another of colorectal cancer patients (van Leersum et al. 2013) found low socio-economic status was associated with increased odds of having one or more comorbidity or multiple comorbidities. Common conditions among the SCLC patients were pulmonary disease, cardiac disease and hypertension, while hypertension and cardiac diseases were also common among colorectal cancer patients. In a Spanish study of colorectal cancer patients in two provinces, congestive heart failure, diabetes and chronic obstructive pulmonary disease were the most common comorbidities among patients (Luque-Fernandez et al. 2020b), while hypertension, diabetes and chronic obstructive pulmonary disease were the three most common comorbid conditions among patients diagnosed with colorectal cancer or with lung cancer in England (Fowler et al. 2020). The prevalence of most of the comorbid conditions studied, and the probability of having the condition as one of multiple comorbidities, was associated with the highest level of socio-economic deprivation. The most frequent conditions in breast cancer patients in the south of the Netherlands were cardiovascular disease, diabetes mellitus and previous cancer (Louwman et al. 2005). Some of the studies of multimorbidity prevalence discuss comorbidity among cancer patients. In a Scottish study, chronic obstructive pulmonary disease (COPD) and diabetes were among the most frequent comorbid conditions present in cancer patients, and the prevalence of the comorbid conditions was higher among the most deprived group of cancer patients, compared with the least deprived group (Barnett et al. 2012). Similar findings to these were reported in a study of multimorbidity in Denmark (Schiotz et al. 2017).

In examining risk factors for development of certain comorbidities, studies of tobacco smoking prevalence in Europe suggest that socio-economic inequalities in smoking were increasing in many countries towards the end of the last century (Giskes et al. 2005). While in northern European countries smoking was more common in lower educated than in higher educated people at that time, the opposite pattern was reported in southern European countries, where smoking was more common in people with higher educational attainment (Cavelaars et al. 2000), particularly women (Huisman et al. 2005). Tobacco control policies introduced in European countries in the 2000s may have helped to reduce the prevalence of smoking in the total population, particularly in lower socio-economic groups, but their effect on the extent of socio-economic inequalities is not clear (Hu et al. 2017). Moreover, socio-economic inequalities in smoking cessation rates increased during the 2000s (Bosdriesz et al. 2015). In a comparative study of forty-three European countries, the countries with the highest summary scores for health policy performance (summarising 10 areas of health policy contributing to major population health gains, including tobacco control) were Nordic countries (Sweden, Norway, Iceland and Finland, in respective order) (Mackenbach and McKee 2013).

22.3. Role of comorbidity as a prognostic factor in cancer outcomes

22.3.1. Comorbidity may influence stage of diagnosis

Fleming posited four hypotheses to explain the relationship between comorbidity and stage at cancer diagnosis (Fleming et al. 2005), and similar ideas have also previously been discussed by others (Kiefe et al. 1998; Newschaffer et al. 1998; Vaeth et al. 2000). These are:

- The 'surveillance' hypothesis: patients with other chronic diseases are likely to have sought medical assistance more often and had more opportunity for early cancer diagnosis.
- The 'physiological' hypothesis: the presence of comorbidity is associated with a more advanced stage of disease. Certain types of comorbidity and cancer may interact at a cellular or physiological level to increase aggressiveness or metastasis of the tumour.
- The 'competing demands' hypothesis: also relates to a more advanced stage of disease, where management of chronic types of comorbidity may divert patient and clinician attention from early symptoms of a tumour.

- The ‘death from other causes’ hypothesis: most applicable to patients with poor prognosis, such as those with a heavy comorbidity burden, where undergoing cancer screening and / or diagnostic testing would not represent a benefit to the patient.

Although the presence of pre-existing comorbidity can be influential in the stage at which a cancer is diagnosed, this may vary according to the type of cancer, the individual comorbid condition, and the overall burden of the comorbidity (Sarfati et al. 2016). Research articles endorse the ‘surveillance’ hypothesis (Fleming et al. 2005; Sarfati et al. 2016; Salika et al. 2018; Renzi et al. 2019a) and the ‘competing demands’ theory (Sarfati et al. 2016; Park et al. 2017). Others suggest that the presence of comorbidity may increase the likelihood of a patient not receiving a stage of disease at diagnosis (Gurney et al. 2015), supporting the ‘death from other causes’ hypothesis. In the case of colorectal cancer, a longer time to diagnosis has been observed in patients with pre-existing comorbid conditions, whether the comorbid condition represented a ‘competing demand’ or an ‘alternative explanation’ to colorectal cancer (Mounce et al. 2017).

Emergency presentation for medical assistance with symptoms of cancer can be a factor in the relationship between comorbidity and stage of cancer diagnosis. Presentation via an emergency hospital admission is most common in patients with serious or complex pre-existing comorbidities (Renzi et al. 2019b) or a higher overall burden of comorbidity (McPhail et al. 2013). In turn, tumour diagnosis via emergency presentation may be associated with later stage of diagnosis (McPhail et al. 2013).

22.3.2. Comorbidity may Influence cancer management and therapeutic options

Comorbid cancer patients may be less likely that those without other chronic diseases to receive curative treatment (Sarfati et al. 2016), although there is some evidence to suggest that patients with comorbidity who receive treatment have better prognosis for survival than those who do not (Sarfati et al. 2009). Decisions to offer treatment to patients may be made based on the type and severity of comorbidity. For example, there is evidence to suggest that the presence of COPD may influence receipt of surgical treatment among early stage non-small cell lung cancer patients (Belot et al. 2019) and influence receipt of adjuvant therapy in colon cancer patients (Gross et al. 2007). Treatment decisions made for comorbid patients may also be influenced by the attitude of physicians – for example, in one study, older physicians were less likely to recommend adjuvant chemotherapy to colon cancer patients compared with younger physicians (Keating et al. 2008). Older age (Mellemgaard et al. 2015), stage at diagnosis (Noer et al. 2017), and socio-economic position (Aarts et

al. 2013b) may influence treatment received by cancer patients with comorbidity, although socio-economic inequalities in cancer management have also been related to age at diagnosis rather than comorbidity status (Rollet et al. 2018).

22.3.2.1. Clinical management of comorbidities with cancer among European countries

Despite the high prevalence of multimorbidity among cancer patients, cancer treatment guidelines generally focus on single-disease management (Guthrie et al. 2012; Tinetti et al. 2012). However, the effective management of multimorbidity is important in optimizing the cancer patient's health status (McLean et al. 2014) and decisions regarding cancer treatment among the elderly cancer patients require careful consideration of comorbidities and multimorbidity (Gurney et al. 2015; Stairmand et al. 2015; Sarfati et al. 2016). Furthermore, postoperative complications occur more frequently in patients with multimorbidity (Søgaard et al. 2013) and certain comorbid conditions have been linked to adverse outcomes following surgery for cancer (Cauley et al. 2015; Sarfati et al. 2016). A challenge for clinicians and oncologists in managing comorbid cancer patients is that health care systems may not be designed for the simultaneous management of two or more chronic conditions (Boyd and Fortin 2010; Barnett et al. 2012; Tinetti et al. 2012). In the United Kingdom, clinical guidelines are not adaptive to the cumulative impact of treatment recommendations on those with multiple chronic conditions, and do not facilitate a comparison of potential benefits or risks (Hughes et al. 2013). A study that investigated the influence of comorbidity on breast cancer treatment and outcomes in 9 European countries concluded that women without comorbidities and of a younger age were most likely to receive prompt, standard treatment for breast cancer (Minicozzi et al. 2019). However, it is unclear from the literature whether the apparent under treatment reflects appropriate consideration of greater toxicity risk, poorer clinical quality, patient preferences, or poor adherence among patients with comorbidity (Søgaard et al. 2013). Ovarian cancer patients in Denmark with moderate or severe comorbidity may often experience longer health system delays then patients with no or mild comorbidity (Noer et al. 2017).

22.4. Comorbidity and cancer survival in Europe

Much of the research conducted in Europe towards understanding the influence the presence of comorbidity has on cancer survival, and on socio-economic inequalities in cancer survival, is based upon studies of patients in the north of Europe. Commonly studied cancers in this context are sex-

specific cancers such as breast or ovarian cancers in women or prostate cancer in men. Within the literature on this topic, studies investigated all-cause survival, survival from the cancer, or both. This section discusses the available scientific literature on the role of comorbidity in cancer survival and also research that investigates how comorbidity may be an influential factor in social inequalities in cancer survival.

22.4.1. Comorbidity and survival

The role of comorbidity in survival following cancer diagnosis is complex. The presence and burden of comorbidity can impact or be impacted by other prognostic factors, such as whether the patient receives curative surgery (Sarfati et al. 2016). Thus, it is plausible to have a scenario where cancer survivors with comorbidities have worse survival than those cancer patients without comorbidities, but more evidence is needed regarding the presence of multimorbidity and cancer survival. Similarly, there are scenarios where cancer survivors with a particular comorbidity and cancer have a better relative survival than those with the same comorbidity yet without cancer, but these scenarios are underreported (Renehan et al. 2019).

In respect to breast cancer prognosis, one study reported little difference in 1-year and 5-year survival between groups of women defined according to their Charlson Comorbidity Index (CCI)(Charlson et al. 1987) score (0, 1 and 2+) (Carlsen et al. 2008), while another reported differences between Charlson score groups and flagged that survival was poorer among patients with comorbid disease (Cronin-Fenton et al. 2007). A study of women with early-stage breast cancer identified that patients with any comorbidities had an increased risk of dying from all causes, but only the presence of peripheral vascular disease, dementia, chronic pulmonary disease, liver disease and renal disease significantly increased the risk of dying due to breast cancer (Ewertz et al. 2018). In studies of women diagnosed with breast cancer in the Netherlands, comorbidity appeared to have an independent prognostic effect on survival (Louwman et al. 2005), except for tumours with poor prognosis (Janssen-Heijnen et al. 2005). Severity or burden of comorbidity was also associated with prognosis (Louwman et al. 2005; Houterman et al. 2004). In a Spanish study of three cancers including breast cancer, 5-year survival decreased as comorbidity burden increased, but stage of diagnosis was the strongest predictor of survival (Parés-Badell et al. 2017).

Among ovarian cancer patients in Denmark, there was evidence to suggest that women with comorbidity had a 17% higher risk of death compared to women without comorbidity, after adjusting for other prognostic factors such as age, stage, residual tumour, histology and performance status (Sperling et al. 2013). Similarly, in another study of ovarian cancer patients in Denmark and Sweden, comorbidity was associated with survival (Noer et al. 2018). Prognosis was poorer among the women in Denmark, although comorbidity did not explain survival differences between the two countries. Comorbidity was also an independent predictor of worse 5-year survival from cancer among surgically treated patients with vulvar carcinoma in Italy (Di Donato et al. 2019).

Among non-small cell lung cancer patients in Denmark, patients with cardiovascular comorbidities (acute myocardial infarction or congestive heart failure) had a 30% excess mortality versus patients without comorbidity, whereas patients with diabetes and patients with cerebrovascular disorders had a 20% excess mortality (Iachina et al. 2015). Severity of comorbidity was prognostic of mortality among resected non-small cell lung cancer patients, and was associated with lower stage-specific 5-year survival in patients with early stage (pT1) disease (Luchtenborg et al. 2012). Conversely, Mellemgaard and colleagues only found comorbidity to have a limited effect on survival only among lung cancer patients treated with chemotherapy (Mellemgaard et al. 2015). In lung cancer patients in France, comorbidity was only associated with lower survival in patients with small cell cancers (Seigneurin et al. 2018).

Severity of comorbidity was associated with lower cancer-related 1-year survival in colorectal cancer patients in England, even after adjusting for age and stage (Shack et al. 2010) and was associated with lower 1-year cancer-related survival in invasive bladder cancer patients in Denmark (Lund et al. 2010). Furthermore, recently it has been shown that multimorbidity significantly increased the time-to-surgery among patients with colorectal cancer in Spain (Luque-Fernandez et al. 2020b). This is possibly because multimorbid patients need to be brought to a healthier status before undergoing a surgical treatment. Also, multimorbidity was a strong independent predictor of short-term mortality at 6 months and 1 year among colorectal cancer patients in Spain (Luque-Fernandez et al. 2020a). Comorbidity was also prognostic of mortality in bladder cancer patients in the Netherlands, after adjusting for other prognostic factors such as age, stage and treatment received (Goossens-Laan et al. 2014).

22.4.2. Comorbidity and social inequalities in survival in Europe

Conclusive information on the underlying causes of social inequalities in cancer survival is sparse. As discussed, comorbidity can interact with tumour characteristics and health care (e.g. receipt of treatment and cancer management) in determining patient prognosis. Furthermore, many studies consider comorbidity in combination with other prognostic factors when investigating social inequalities in cancer survival. Different approaches to defining and measuring comorbidity, and variation in measures (or proxy measures) of social or socio-economic position can limit the opportunity to draw comparisons across the literature.

We have summarised the published studies reporting on the potential role of comorbidity on the social gradient in cancer survival in European countries (Table 22.1). The results presented in many of these studies were in a format that showed differences in survival or mortality between social groups following progressive adjustment for comorbidity and other factors in the analysis models. Where possible, we calculated the percentage change of social inequalities in the outcome reported using the equation $([HR_{Basic\ model} - HR_{Basic\ model\ +\ comorbidity}])/[HR_{Basic\ model} - 1] \times 100$, an approach used in a published review of socio-economic inequalities in prostate cancer survival (Klein and von dem Knesebeck 2015). Of the studies found (n=14), half of the studies were of female cancers: breast (Aarts et al. 2011; Larsen et al. 2015; Morris et al. 2016; Morris et al. 2017), cervical (Ibfelt et al. 2013), endometrial (Seidelin et al. 2016) or ovarian (Ibfelt et al. 2015) cancer. The remaining were prostate (Li et al. 2012; Aarts et al. 2013b), colorectal (Frederiksen et al. 2009a; Frederiksen et al. 2009b), or lung cancer (Dalton et al. 2015), or studies of more than one type of cancer (Aarts et al. 2013a; Louwman et al. 2010). The studies were undertaken in the north of Europe: in Denmark (n=7), England (n=2), Netherlands (n=4) and Sweden (n=1).

The contribution of comorbidity in reducing social inequalities in breast cancer survival was similar among screen detected and non-screen detected patients in the Netherlands (Aarts et al. 2011) and in England (Morris et al. 2016): comorbidity was responsible for approximately 20% and 10% of socio-economic inequalities in these groups, respectively, in both countries.

Table 22.1 Research articles discussing comorbidity and social inequalities in cancer survival or mortality, according to cancer type

Authors	Cancer	Country	Study population	Study period	Measure of Comorbidity	Measure of social position	Other covariates	Outcome, measure	Percentage change of social inequalities in outcome due to comorbidity†◊	Findings
Female cancers										
Aarts et al. (2011)	Breast	Netherlands	Women invited for mass breast cancer screening in southern Netherlands	1998 - 2006	Charlson Comorbidity Index (CCI)	SES indicator by postal code (mean household income, mean economic value of house)	Age Stage Therapy	Mortality (cancer-specific), Hazard Ratios (HR)	**SES** inequalities Screen-detected: -23% (**1.30** to **1.23**) Interval cancer: -7% (**1.72** to **1.67**) Not screened: -12% (**1.42** to **1.37**)	Comorbidity explained most of the socio-economic inequalities in survival among screen-detected patients
Larsen et al. (2015)	Breast	Denmark	Postmenopausal women with breast cancer identified from Danish Diet, Cancer and Health Study	December 1993 - May 1997	CCI: one year before cancer diagnosis Diabetes: at diagnosis	Educational attainment Income	Age Disease-related prognostic factors (tumour size, lymph node status, no. positive lymph nodes, malignancy grade, estrogen receptor status)	Mortality (all-cause), HR	**Education**: -6% (**1.35** to 1.33) **Income**: -89% (1.09 to 1.01)	Comorbidity and other prognostic factors affected but did not explain the social gradient in death after breast cancer
Morris et al. (2016)	Breast	England	Women diagnosed with breast cancer aged 50-70 years in the West Midlands region of England	1989 - 2011	CCI score (continuous)	Deprivation (Income domain of Indices of Multiple Deprivation)	Age Year of diagnosis Extent of disease Tumour size Histology Surgery Time to surgery	Mortality (cancer-specific) at five years after diagnosis, HR	Non-screen detected women: -11% (**1.44** to **1.39**) Screen-detected: -18% (**1.66** to **1.54**)	Adjustment for comorbidity resulted in a slight change in excess hazard of death in the most deprived women in both non-screened and screened groups
Morris et al. (2017)	Breast	England	Screening-eligible women diagnosed with breast cancer aged 50-70 years in the West Midlands region of England	1989 - 2006	CCI score (0, 1+)	Deprivation (Income domain of Indices of Multiple Deprivation)	Analysis stratified by each factor of interest in turn	Net survival, %	Calculation not possible as data not provided	Persistent trend of lower net survival for more deprived women, irrespective of comorbidity status and other factors studied (obesity, alcohol intake and smoking status)

Authors	Cancer	Country	Study population	Study period	Measure of Comorbidity	Measure of social position	Other covariates	Outcome, measure	Percentage change of social inequalities in outcome due to comorbidity†◊	Findings
Ibfelt et al. (2013)	Cervical	Denmark	National: women diagnosed with cervical cancer	2005 - 2010	CCI score (0, 1, 2, ≥3) up to one year before cancer diagnosis	Educational attainment Disposable income Cohabitation status	Education adjusted for age Cohabitation status adjusted for age and education Income adjusted for age, education and cohabitation status	Mortality (all-cause), HR	**Education**: -4% (**1.46** to **1.44**) **Disposable income**: ALL: +6% (**1.32** to **1.34**) Age <60: -5% (**1.59** to **1.56**) **Cohabitation status**: ALL: -88% (1.08 to 1.01) Age < 60: -2% (**1.60** to **1.59**)	Socio-economic differences in survival partly explained by stage and less by comorbidity
Seidelin et al. (2016)	Endometrial	Denmark	National: women diagnosed with endometrial cancer	2005 - 2009	CCI one year before cancer diagnosis	Educational attainment	Age Cohabitation BMI Smoking status	Mortality (all-cause), HR	**Education**: -4% (**1.49** to **1.47**)	Social inequalities in survival were not reduced by adjustment for cohabitation status, BMI, smoking and comorbidity, only by further adjustment for stage.
Ibfelt et al. (2015)	Ovarian	Denmark	National: women diagnosed with ovarian cancer	2005 - 2010	CCI score (0, 1, 2, ≥3) up to one year before cancer diagnosis Diabetes at diagnosis	Educational attainment Cohabitation status Disposable income	Education adjusted for age, Cohabitation status adjusted for age and education, Income adjusted for age, education and cohabitation status Analysis stratified by stage	Mortality (all-cause), HR	**Education**: Stage I + II: -4% (**1.75** to **1.72**) Stage III + IV: -6% (1.17 to 1.16) **Cohabitation status**: Stage I + II: +3% (1.38 to 1.39) Stage III + IV: 0% (1.24 to 1.24) **Disposable income**: Stage I + II: -10% (**1.80** to **1.72**) Stage III + IV: -2% (0.97 to 0.99)	Socio-economic differences in survival persisted after adjustment for comorbid conditions, stage, histology operational status and lifestyle factors.
Male cancers										
Aarts et al. (2013b)	Prostate	Netherlands	Men diagnosed with prostate cancer in the south-eastern Netherlands (Eindhoven Cancer Registry region)	1998 - 2008	CCI (adapted to include additional conditions)	SES indicator by postal code (mean household income, mean economic value of house)	Stage Age Year of diagnosis Therapy / treatment	Overall 10-year survival Mortality (all-cause assumed)	Localised stage: ≤59 years: -21% (**2.32** to **2.04**) 60-74 years: -25% (**1.81** to **1.61**) Advanced stage: 60-74 years: -6% (**1.36** to **1.34**)	Socio-economic differences in 10-year survival were related to treatment and comorbidity

Authors	Cancer	Country	Study population	Study period	Measure of Comorbidity	Measure of social position	Other covariates	Outcome, measure	Percentage change of social inequalities in outcome due to comorbidity†◊	Findings
									≥75 years: -15% (**1.27** to **1.23**)	
Li et al. (2012)	Prostate	Sweden	Male population of Sweden aged 25 to 74 years	1990 - 2008	Previous hospitalisation for chronic obstructive pulmonary disease	Neighbourhood deprivation index, based on low education status, low income, unemployment, social welfare assistance	Year of diagnosis Analysis stratified by age and stage Marital status Immigrant status Urban / rural status Mobility	Mortality (cancer-specific), Odds Ratio (OR)	Calculation not possible for comorbidity in isolation: model adjustment made for hospitalisation for COPD plus marital status, family income, educational attainment, immigrant status, urban / rural status and mobility	Men who were older, unmarried, with a low family income or low educational attainment, had moved or been hospitalised for COPD had highest odds of all cause mortality.
Other cancers										
Frederiksen et al. (2009a)	Colorectal	Denmark	Patients diagnosed with colon or rectal cancer, recorded in the national clinical database of Danish Colorectal Cancer Group (~93% of patients in Denmark with first-time adenocarcinoma of the rectum or colon)	May 2001 - December 2004	Dichotomous comorbidity variables: i)medical treatment for cardiovascular diseases, ii) hospitalisation for cardiovascular diseases, iii) medication treatment / hospitalisation for COPD, iv) medical treatment / hospitalisation for diabetes, v) medical treatment or hospitalisation for depression or schizophrenia, vi) medical treatment or hospitalisation for liver, kidney or connective tissue diseases (other)	Annual income Educational attainment Housing status Cohabitation status	Alcohol intake Smoking status BMI Income adjusted for age, sex, year of operation, cohabiting status and education Education is adjusted for age, sex, year of operation Housing status is adjusted for age, sex, year of operation, cohabiting status, education and income Sex Year of operation	Mortality (all-cause), HR	Education: -40% (**0.80** to **0.88**)* Housing status: -30% (**0.87** to **0.91**)*	The association between SES and all-cause mortality was partly mediated through lifestyle and comorbidity
Frederiksen et al. (2009b)	Colorectal	Denmark	Patients undergoing elective surgery for colorectal cancer,	May 2001 - December 2004	Dichotomous comorbidity variables: i)medical treatment for cardiovascular diseases,	Educational attainment	Age Sex Year of operation Alcohol intake	30-day post-operative mortality (cancer-specific), HR	Education: -37% (**0.65** to **0.78**)* Housing status: -42% (**0.76** to 0.86)*	The social gradient in 30-day postoperative mortality was accounted for by

Authors	Cancer	Country	Study population	Study period	Measure of Comorbidity	Measure of social position	Other covariates	Outcome, measure	Percentage change of social inequalities in outcome due to comorbidity†◊	Findings
			recorded in the national clinical database of Danish Colorectal Cancer Group (~93% of patients in Denmark with first-time adenocarcinoma of the rectum or colon)		ii) hospitalisation for cardiovascular diseases, iii) medication treatment / hospitalisation for COPD, iv) medical treatment / hospitalisation for diabetes, v) medical treatment or hospitalisation for depression or schizophrenia, vi) medical treatment or hospitalisation for liver, kidney or connective tissue diseases (other)		Smoking status BMI			comorbidity and lifestyle, but not by treatment and disease factors
Dalton et al. (2015)	Lung	Denmark	Patients diagnosed with lung cancer	2004 - 2010	CCI score (0, 1-2, ≥3)	Income Educational attainment Cohabitation status	Age Sex Period of diagnosis Performance status Stage Receipt of first-line treatment	Mortality (all-cause), HR	Calculation not possible for comorbidity in isolation: model adjustment made for comorbidity plus stage, first-line treatment and performance status	Socio-economic differences in survival partly explained by differences in stage, treatment and comorbidity
Studies of more than one cancer										
Aarts et al. (2013a)	Breast, prostate, NSCLC,	Netherlands	Patients diagnosed with cancer in the south-eastern Netherlands (Eindhoven Cancer Registry region)	1991 - 2008	CCI	Educational attainment	Baseline characteristics: Age Year of diagnosis Stage at diagnosis Lifestyle behaviours	Mortality (all-cause assumed), HR	Prostate cancer: Adjusting only for baseline characteristics: -10% (**2.9** to **2.7**) Adjusting for baseline characteristics and lifestyle behaviours: +5% (**3.00** to **3.01**)	Presence of comorbidities, physical activity levels and smoking status affected survival from prostate cancer, these factors did not contribute to educational inequalities in survival.
Louwman et al. (2010)	Oesophagus, stomach,	Netherlands	Patients diagnosed with cancer in the	1997 - 2006	Presence of comorbidity	SES indicator by postal code (mean	Age Stratified by cancer and by sex	Mortality (all-cause), HR	Colorectal cancer: Males: -23% (**1.13** to **1.10**) Females: -33% (1.09 to	Comorbidity partly explained socio-economic

Authors	Cancer	Country	Study population	Study period	Measure of Comorbidity	Measure of social position	Other covariates	Outcome, measure	Percentage change of social inequalities in outcome due to comorbidity†◊	Findings
	colon or rectum, pancreas, lung, melanoma, breast, cervix uteri, corpus uteri, ovary, prostate, bladder, kidney, and non-Hodgkin's lymphoma (NHL)		south-eastern Netherlands (Eindhoven Cancer Registry region)			household income, mean economic value of house)			1.06) Lung: Males: 0% (**1.11** to **1.11**) Females: 0% (**1.09** to **1.09**) Prostate (males): 23% (**1.47** to **1.36**) Breast (females): 18% (**1.68** to **1.56**) All cancers studied combined: Males: -12.5% (**1.40** to **1.35**); Females: -15% (**1.40** to **1.34**)	inequalities in 1-year survival among patients with colorectal, prostate or breast cancers. The gradient of more comorbidity from high to low SES was apparent for all tumour types studied.

† Comparing low versus high measure of social position, unless otherwise indicated; ***** Comparing high versus low measure of social position

◊ Statistically significant results are in bold

Abbreviations: BMI: Body Mass Index; CCI: Charlson Comorbidity Index; HR: Hazard ratio; NHL: Non-Hodgkin lymphoma; OR: Odds ratio; SES: Socio-economic status

Some studies stratified their analyses by stage, reporting results for localised / stage I or II cancer and for advanced / stage III or IV cancer. Adjustment for comorbidity resulted in a larger reduction in socio-economic inequalities in survival among prostate cancer patients (Aarts et al. 2013b) - and inequalities in survival according to income among ovarian cancer patients (Ibfelt et al. 2015) - with an earlier rather than later stage of diagnosis. For example, after adjustment for comorbidity, socio-economic inequalities reduced by 25% among patients aged 60-74 years with localised stage prostate cancer, while the reduction was 6% among patients of the same age with advanced stage of disease. Comorbidity appeared to account for more of the inequalities in survival according to disposable income and cohabitation status among cervical cancer patients aged under 60 years compared with patients of all ages (Ibfelt et al. 2013). However, among prostate cancer patients, the extent of the contribution of comorbidity toward socio-economic inequalities in survival appeared to increase with increasing age, particularly among patients with advanced stage of disease (15% of inequalities among patients aged 75 years or older compared with 6% of inequalities among patients aged 60-74 years) (Aarts et al. 2013b).

There are limitations in drawing conclusions upon the role of comorbidity in social inequalities in cancer survival from the findings of these studies. Of the fourteen studies, only five explicitly stated that results provided were for cancer-specific mortality or survival due to cancer. Of the remaining studies, seven presented results for all-cause mortality and the other two did not specify (all-cause mortality was assumed in these instances). Another limitation is that, based on the methods of analysis used in these studies, the application of causal assumptions to the associations reported is not valid. In Fig. 22.1, the Directed Acyclic Graph illustrates assumed causal relationships between variables in the pathway between social position and cancer survival. To be able to examine and quantify the causal effect of comorbidity and associated variables in this pathway would require analytical approaches such as causal mediation analysis.

22.5. Proposing the need for life tables by deprivation

When interest is in survival from the cancer (e.g. net survival), competing risks of death from other causes need to be accounted for. As information on cause of death contained in routine, population-based data is not considered to be robust and accurate enough, the risk of death from other causes is estimated from life tables of the general population with socio-demographics similar to the cancer patients. Life tables provide average mortality rates for a geographic area, most commonly according

to sex and age. However, when examining the role of comorbidities on social inequalities in cancer survival, it is important that the life tables reflect the social differential in mortality rates observed in the general population. General life tables systematically underestimate the expected mortality hazards among more deprived populations and overestimate these in less deprived. Using such general life tables can therefore result in underestimated net survival (i.e. survival from cancer) in deprived populations and overestimated net survival in less deprived populations (Dickman et al. 1998; Maringe et al. 2008). Furthermore, a simulation-based study showed that the use of life tables lacking stratification by a variable present in the excess hazard model leads to measurement bias in both the effect of this variable and other variables included in the model (Graffeo et al. 2012).

Some strategies have been proposed to compensate for insufficient stratification of life tables. Sensitivity survival analyses can be performed using modified life tables according to successive plausible scenarios regarding the social gradients in the studied population (Ito et al. 2014; Antunes et al. 2019).

Rubio and colleagues developed models for the estimation of the excess mortality hazard that correct for possible misspecification of the expected mortality rate occurring due to mismatches in the life table (Rubio et al. 2019). Flexible population-based models were developed to account for cause-of-death misclassification and for the effects of selection when estimating long-term net survival in the clinical trial setting (Goungounga et al. 2019).

Similarly, life tables that do not account for comorbidities may overestimate the expected survival in populations with an important burden of comorbidities while underestimating expected survival in populations with a low prevalence of comorbidities. Life tables commonly include the deprivation dimension in the UK and in several countries of the North of Europe. Whether such life tables (which may also include ethnicity) are sufficient to adjust for social differential mortality associated with comorbidity is still debated. A study focussing on the specific lung and laryngeal cancers (for which most patients have comorbidities associated with tobacco smoking) concluded that not using life tables adjusted for tobacco smoking (and deprivation) led to notable under-estimation of cancer survival for all deprivation groups, but had a fairly small impact on the estimation of the deprivation inequalities in cancer survival (Ellis et al. 2014). Life tables adjusted for comorbidity may nevertheless be helpful to uncover the role of comorbidity in social inequalities in cancer survival. Such life tables are available in the USA (Mariotto et al. 2013).

22.6 Conclusions

Among the published studies on this topic in a European setting, the magnitude of the influence of comorbidity in social inequalities in cancer survival varied. The extent of the relationship also varied by measure of social position. The impact comorbidity had on inequalities in survival was also associated with other prognostic factors, such as tumour stage, patient age, and treatment received.

Having one or more comorbid conditions at the time of cancer diagnosis is associated with socio-economic position, and the prevalence of many comorbid conditions increases with increasing levels of socio-economic deprivation (Barnett et al. 2012; van Leersum et al. 2013; Aarts et al. 2015; Schiotz et al. 2017; Fowler et al. 2020). The most deprived groups of patients may be disproportionately impacted by clinical guidelines that focus on single disease management and by decision making that leads to non-treatment of cancer patients with comorbidity.

Reviewing the treatment process of cancer patients with comorbidity may help to reduce socio-economic inequalities in receipt of treatment, and ultimate prognosis. Clear guidelines that account for multiple management scenarios (depending on comorbidity severity and stage of cancer), together with the resources to robustly manage comorbid conditions during cancer treatment, could help reduce adverse outcomes occurring due to the comorbid disease, and limit the development of new comorbidities. Moreover, investigation of aspects of comorbidity management, such as the relationship between adherence to comorbidity medication and outcomes among cancer patients, may be informative. In a study of patients with diabetes and ischemic heart disease, cardioprotective medication adherence was associated with lower all-cause mortality (Ho et al. 2006).

Further studies investigating comorbidity and social inequalities in cancer survival across multiple European countries, with representation of southern European countries, would provide a firmer foundation for comparison of inequalities between countries. Greater efforts in achieving a more consistent approach toward measuring comorbidity would help facilitate a like-for-like comparison.

From the evidence presented, the need for a mechanistic understanding of the causes of socio-economic inequalities in survival outcomes is apparent. The current lack of understanding illustrates the importance of using causal inference methods with routine medical data and population-based registries to disentangle the contributions of different pathways of cancer diagnosis and treatment to these inequalities in cancer survival (Li et al. 2016).

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Comorbidity and colon cancer outcomes

Drawing from the scientific literature discussed in the book chapter, there is clear evidence to suggest comorbidity influences survival or mortality from many of the cancer types, including breast cancer,[86-89] ovarian cancer[90] and non-small cell lung cancer.[91, 92] This was also reported in studies of colon or colorectal cancer patients, both in Europe[48, 52, 56, 93] and further afield. For example, studies of colorectal cancer patients in the United States[94] and South Australia[95] reported that comorbidity status was associated with 5-year cancer-related mortality. In the latter study, post-operative patients with multiple or severe comorbidities had a 21% increased risk of 5-year mortality compared with patients with no comorbidity.[95] Comorbidity status was also associated with 5-year all-cause mortality in a study of colon cancer patients in New Zealand.[96] In this study, patients with Chronic Respiratory Disease , Myocardial Infarction or with Congestive Heart Failure had approximately 20-25% increased risk of 5-year all-cause mortality of that of patients without the respective condition. Meanwhile patients with angina had a 12% reduced risk of mortality versus those patients without angina.

Additionally, comorbidity status has been linked with shorter-term prognosis among colorectal cancer patients. In a study in England, patients with a Charlson Comorbidity Index (CCI) score of 3 or more had an 80% increased risk of mortality within one year of colorectal cancer diagnosis compared with patients with a score of 0, after adjusting for age, stage, deprivation and follow-up.[48] Comorbidity level, measured in terms of number of comorbid conditions, was an independent predictor of one-year mortality in a study of patients in the United States. Compared with patients with no comorbidity, patients with 2 comorbid conditions had a 32% increased risk and patients with 3 or more conditions a 48% increased risk of one-year mortality.[97] Having more than one comorbidity was also a predictor of six-month and one-year mortality among colorectal cancer patients in a study conducted in Spain.[98]

Comorbidity and social or socio-economic inequalities in colon cancer mortality

Published studies investigating the influence of comorbidity on social inequalities in cancer prognosis are scarce. Three studies reported results on differences in survival or mortality between social groups of colorectal cancer patients in European countries. Two were studies in Denmark, one of which focused on 30-day post-operative cancer-related mortality of patients undergoing elective surgery for colorectal cancer[56] and the other all-cause mortality among colorectal cancer patients.[52] The third investigated all-cause mortality for several cancers, including colorectal cancer, in the Netherlands.[93] The results presented in these studies are summarised in Table 22.1 within the book chapter. Among patients studied in Denmark, adjusting for comorbidity reduced the odds of thirty-day post-operative cancer-related mortality according to education status by 37% (from 35% to 22% increased odds of mortality among patients with short versus longer educational attainment) and according to housing status by 42% (from 24% to 14% increased odds of mortality among patients renting their home versus owning it).[56] Adjusting for comorbidity reduced the hazard of all-cause mortality according to education status by 40% (from 20% to 12% increased hazard of mortality, short versus long education) and by 30% according to housing status (from 13% to 9% increased hazard of mortality among renters versus owners).[52] There is also evidence from the Netherlands to suggest that adjusting for comorbidity reduced socio-economic differences in all-cause mortality by 23% among male colorectal cancer patients (from 13% to 10% increased hazard of mortality of patients with low versus high SES), although the evidence of comorbidity reducing SES inequalities among females was weak.[93] All three studies concluded that comorbidity (together with lifestyle factors in the Danish studies) had partly mediated the association between social position and the respective mortality outcome.

However, two studies of comorbidity and colorectal cancer survival from the United States do not support these conclusions. Robbins et al investigated insurance status, comorbidity and survival among black and white colorectal cancer patients. Comorbidity influenced survival but had little

impact on differences in survival according to various measures of social position, such as household income or attainment of a high school degree and survival, irrespective of race.[97] Similarly, another study reported only weak evidence of an association between socio-economic status and colorectal cancer mortality, and adjusting for comorbidity did not have any effect on this association.[99]

When estimating cancer survival, using lifetables adjusted for comorbidity would be useful to account for background mortality due to these comorbidities. Lifetables that do not adjust for comorbidity may overestimate the expected survival in populations with a higher burden of comorbidity and underestimate survival in populations with less comorbidity. As discussed in the book chapter, lifetables including deprivation may account for some of the differential distribution of comorbidity. The use of comorbidity-adjusted lifetables is not commonplace, partly as opportunities to construct these lifetables are dependent on the availability and reliability of information on comorbidity. In the United States, Mariotto and colleagues developed non-cancer lifetables by comorbidity score, but as comorbidity data was derived from Medicare claims data it was limited to people aged 66 years of age or older.[100]

Given the scarcity of published studies, plus differing measures of social or socio-economic position and varying measures of outcome within the available scientific literature, there is a gap in the knowledge regarding the role that comorbidity plays in socio-economic inequalities in cancer outcomes. Further research into this topic is important and timely given the increasing prevalence of chronic disease and multimorbidity, the association between lower socio-economic position and chronic disease prevalence, and the persistence of socio-economic inequalities in cancer outcomes.

Chapter 3 - Influence of prognostic factors in socio-economic inequalities in short-term cancer mortality

This chapter covers the research conducted to complete the first objective of this thesis: to examine ninety day mortality among colon cancer patients according to socio-economic position, and to investigate the extent to which prognostic factors such as age, stage at diagnosis, comorbidity and receipt of surgical treatment influence inequalities in ninety-day mortality. This work was published in the British Journal of Cancer in 2017.[101] The chapter includes the publication and supplementary material, a background to the work, a description of the study, the main findings and conclusions, and a discussion explaining how this work fulfils the first objective of this thesis.

Introduction to research paper 1

Background

Colon cancer is one of the most commonly diagnosed cancers in England among adults, but has a less favourable short-term prognosis than other common cancers.[102] Additionally, wide socio-economic inequalities in survival from cancer of the colon have persisted for some time,[8, 10, 11] with inequalities most evident in the short-term after diagnosis.[12]

Within the scientific literature, socio-economic position has been investigated alongside other factors that may influence colon or colorectal cancer mortality. For example, studies have focused on age[103] or stage at diagnosis[12, 47] as prognostic factors, or have examined prognostic factors in short-term mortality following surgery for colon cancer.[57, 58] However, few studies offer a comprehensive

assessment of prognostic factors influencing socio-economic inequalities in short-term colon cancer mortality among all patients.

The aim of this study was to quantify differences in ninety-day mortality (i.e. death occurring within ninety days of cancer diagnosis) according to socio-economic position, and to investigate how the prognostic factors of patient comorbidity, age, stage at diagnosis, receipt of major surgery (curative intent assumed) and presentation for surgery contribute to the differences in mortality between socio-economic groups, according to sex.

Materials and Methods

To fulfil this aim I undertook a population-based study of patients diagnosed with colon cancer in England between 1st January 2010 and 31st March 2013 using National Cancer Registry data for England linked with National Bowel Cancer Audit data and Hospital Episode Statistics. In this study, the measure of socio-economic position was the deprivation group that the patient belonged to, based on their residential postcode at the time of cancer diagnosis. Deprivation group was defined using the Income domain of the English Indices for Multiple Deprivation 2010,[79] which provides a relative measure of deprivation at the Lower layer Super Output Area (LSOA) level. Patient comorbidity was measured as a score, based on the presence of 17 conditions of the Charlson Comorbidity Index (CCI)[83] and their assigned weightings. The four-category comorbidity score variable used in the analysis summarised this CCI score (i.e. according to whether it was 0, 1, 2 or 3 or more).

For each sex (referred to as 'gender' in the paper published in the British Journal of Cancer) I used logistic regression models to estimate two different indicators of probability of death within ninety days of cancer diagnosis.

The first indicator was the conditional probability of death, which provided the probability of death of each deprivation group at every possible combination of values of the prognostic factors. From this

indicator it was possible to compare the difference in the probability of death between the most deprived patients with that of the least deprived patients, according to specific values of patient age, comorbidity score, stage of diagnosis and surgical treatment received.

The second indicator was the average predicted probability of death within ninety days of diagnosis. It was estimated for each deprivation group and was an average of the predicted probability of death of every patient in that group. In the first instance it was estimated based on the observed value of the deprivation group (i.e. between 1 and 5, depending on the relative deprivation level), with the distribution of prognostic factors among patients in that group remaining as observed. This indicator provided the means to calculate the difference in probability of death between the most and least deprived groups, after adjustment for the differential distribution of prognostic factors among patients in each group.

The average predicted probability of death was then estimated again for each of the groups, but with the assumption the patients in each group belonged to the least deprived group (group 1), while the distribution of prognostic factors remained as observed. For each deprivation group, the resulting change in the probability of death gave an indication of the effect of deprivation within that group. This also allowed for comparison of the differences in probability of death of the most and least deprived groups, with and without accounting for the effect of deprivation. Further analyses explored prognostic factors contributing to residual differences in probability of death between the most and least deprived groups of patients after accounting for the effect of deprivation.

Main findings

The research findings of this study were reported in the paper "Persistent inequalities in 90-day colon cancer mortality: an English cohort study", published in the British Journal of Cancer in 2017.[101] I also presented the research findings at scientific conferences (details provided in the Appendices).

The results obtained from this study showed that the most deprived patients were more likely to die within ninety days of cancer diagnosis than the least deprived patients, even after adjusting for prognostic factors. Based upon the conditional probability of death, older age, advanced stage and the highest comorbidity score (3 or higher) were strong prognostic factors of ninety-day mortality, as was receiving major surgery via emergency presentation. The magnitude of the socio-economic differences in probability of death within ninety days varied according to the values of prognostic factors. Inequalities were wider among patients with older age, advanced stage, higher levels of comorbidity or who received emergency surgery.

At the deprivation group level, after adjusting for the distribution of values of prognostic factors of patients within that group, the difference in the average predicted probability of death of the most deprived group and the least deprived group of male and of female patients was 5.3% and 6.5%, respectively. When the probability of death was estimated with the assumption that all patients were in the least deprived group (distribution of other prognostic factors remaining unchanged), the difference between the most and least deprived groups reduced. Among male patients, the difference between these groups reduced to 1.3% and among female patients the difference became 1.7%. Further analysis exploring the contribution of prognostic factors to these residual differences showed that stage and treatment in combination were the most influential factors: differences became 0.1% among males and 0.3% among females when excluding these variables from the models.

Conclusion

The most deprived patients consistently had poorer prognosis then the least deprived patients, regardless of the status of other prognostic factors at which probability of death was estimated. At the deprivation group level, accounting for the effect of deprivation reduced but did not completely remove the differences in ninety-day mortality between the most and least deprived groups. Differential distribution of prognostic factors in deprivation groups may account for some of the mortality differences between the most and least deprived groups. Stage and treatment appeared to be the prognostic factors that had the most influence on the remaining socio-economic inequalities after the effect of deprivation was taken into account.

Fulfilment of the first objective of this thesis

In this chapter I quantified the probability of death within ninety days of colon cancer diagnosis among the most and the least deprived groups of patients at every combination of values of the prognostic factors. I also estimated the probability of death at deprivation group level, adjusting for the distribution of the prognostic factors within that group. I have shown that socio-economic inequalities in ninety-day mortality among colon cancer patients exist, and while comorbidity score, stage, age and receipt of major surgery are all prognostic factors in ninety-day mortality, they did not fully explain differences in probability of death between the most and least deprived groups of patients.

The results indicated that patient comorbidity, measured according to the CCI index score, was an influential factor in ninety-day mortality, particularly among the most deprived group of patients: those with the highest comorbidity score had a higher probability of ninety-day mortality than patients with no recorded comorbidity, and the presence of comorbidity appeared to have the greatest impact on ninety-day mortality amongst those in the most deprived groups. While the CCI is commonly used in epidemiological research of cancer outcomes, there is no one recommended measure of comorbidity in the cancer setting.[104] One limitation of using a summary measure of patient

comorbidity is that it does not provide information on the comorbid condition(s) the patient has, nor their specific influence on the patient's outcome. In view of this limitation, the following chapters of this thesis investigate comorbidity at a more detailed level.

In the next chapter I examine patterns in the prevalence of comorbidities among cancer patient populations according to socio-demographic characteristics, and evaluate hospital-based electronic health records as a source of information on chronic disease prevalence (**Chapter 4**). To further disentangle the role of comorbidity in socio-economic inequalities in short-term colon cancer mortality, I then investigate the influence of severity of comorbidity on ninety-day mortality by deprivation group. Time since specific comorbid conditions were recorded, and duration and frequency of hospital visits once the condition is present are used as proxies for comorbidity severity (**Chapter 5**).

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Helen Fowler
Principal Supervisor	Bernard Rachet
Thesis Title	The role of comorbidity in socioeconomic inequalities in short-term mortality among colon cancer patients in England

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	British Journal of Cancer		
When was the work published?	August 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of the paper. I conducted the literature review and carried out the data analysis. I prepared all drafts of the paper. The co-authors provided input and feedback on the analysis strategy and on the drafts of the paper that I had prepared.

Student Signature: [redacted] **Date:** 16/10/20

Supervisor Signature:  **Date:** 19 October 2020

FULL PAPER

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Persistent inequalities in 90-day colon cancer mortality: an English cohort study

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Background: Variation in colon cancer mortality occurring shortly after diagnosis is widely reported between socio-economic status (SES) groups: we investigated the role of different prognostic factors in explaining variation in 90-day mortality.

Methods: National cancer registry data were linked with national clinical audit data and Hospital Episode Statistics records for 69 769 adults diagnosed with colon cancer in England between January 2010 and March 2013. By gender, logistic regression was used to estimate the effects of SES, age and stage at diagnosis, comorbidity and surgical treatment on probability of death within 90 days from diagnosis. Multiple imputations accounted for missing stage. We predicted conditional probabilities by prognostic factor patterns and estimated the effect of SES (deprivation) from the difference between deprivation-specific average predicted probabilities.

Results: Ninety-day probability of death rose with increasing deprivation, even after accounting for the main prognostic factors. When setting the deprivation level to the least deprived group for all patients and keeping all other prognostic factors as observed, the differences between deprivation-specific averaged predicted probabilities of death were greatly reduced but persisted. Additional analysis suggested stage and treatment as potential contributors towards some of these inequalities.

Conclusions: Further examination of delayed diagnosis, access to treatment and post-operative care by deprivation group may provide additional insights into understanding deprivation disparities in mortality.

Colon cancer, the fourth most frequently diagnosed cancer in England, has a less favourable 1-year prognosis in England when compared with some other common cancers, such as cancers of the rectum and breast (Exarchakou *et al*, 2015). One-year net survival for colon cancer (i.e., the survival of colon cancer if the other causes of death have been removed) was recently reported at around 75%, while it was largely >80% for the other cancers mentioned above (Exarchakou *et al*, 2015). Meanwhile, wide socio-economic inequalities in survival from colon cancer have been repeatedly reported in England (Mitry *et al*, 2008; Rachet *et al*, 2010), with worse prognosis for more deprived patients. These inequalities are generally evident shortly after diagnosis (Møller *et al*, 2012), with two-thirds of cancer deaths related to these inequalities occurring within 6 months after diagnosis (Ellis *et al*, 2012). Socio-economic inequalities in colon cancer survival have been reported in several countries (Wrigley *et al*, 2002; Aarts *et al*, 2010; Cavalli-Bjorkman *et al*, 2011; Ito *et al*, 2014) but have not been found in others (Dejardin *et al*, 2013; Antunes *et al*, 2016), which underlines the importance of understanding factors contributing to inequalities and more particularly differential short-term mortality in colon cancer patients in England.

Many published studies have focussed their attention exclusively towards subgroups of colon cancer patients, such as postoperative patients (Morris *et al*, 2011) or elderly postoperative patients (Dekker *et al*, 2011), to explain differences in short-term survival. A variety of indicators has been considered in studies examining SES – from metrics such as patient occupation or education level to deprivation indices. Common themes in the literature include examining the relationship between age, stage at diagnosis and short-term mortality (Gatta *et al*, 1998; Møller *et al*, 2012) and the relationship between cancer treatment and short-term mortality (Faivre *et al*, 2007). However, there was little discussion offered

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regarding the relationship between socio-economic status and risk factors for short-term mortality, such as comorbidity or stage at diagnosis. Awareness of factors contributing to different prognoses for short-term survival across all patient populations is central to the effective management of cancer care.

This study aims to quantify differences in 90-day mortality following diagnosis of colon cancer according to patients' socio-economic status. We investigate to what extent these differences are influenced by age, stage at diagnosis, patient comorbidity score, whether the primary treatment received by the patient was a major surgery and whether the patient received major surgery as an elective or emergency procedure.

MATERIALS AND METHODS

Data. The analysis was undertaken on 69 769 adults aged 15–99 years diagnosed with colon cancer in England between 1 January 2010 and 31 March 2013 and followed up until 31 December 2014. The data for these analyses were obtained from the national cancer registry records (Office for National Statistics, 2014) linked with Hospital Episode Statistics (HES) records (Health and Social Care Information Centre, 2013) and national bowel cancer clinical audit data (Health and Social Care Information Centre, 2014a) – representing information collated from clinicians working in multidisciplinary teams who have direct involvement with the patients. The linkage of the registry data with clinical audit data and HES records was undertaken using an algorithm developed by the Cancer Survival Group at the London School of Hygiene and Tropical Medicine (Shack, 2009), which prioritised linkage of records according to the combination of patient identifier variables (Office for National Statistics, 2014). The cancer registry data represented $>99\%$ of cancer registrations in England (Office for National Statistics, 2014) and provided information on gender, age at diagnosis, socio-economic status, tumour stage and date of diagnosis. The clinical audit data had a case ascertainment of 94% (Health and Social Care Information Centre, 2014b) and captured information on tumour stage and treatment. To obtain the most robust information on stage at diagnosis from clinical audit and registry data, we used an algorithm (Benitez-Majano *et al*, 2016) that creates a composite stage at diagnosis variable, based on the rules of the Union for International Cancer Control TNM classification of malignant tumours. It combined available information in individual tumour (T), nodes (N) and metastases (M) stage components, prioritising information captured in the clinical audit data and only using registry stage data where this was not present, to derive a four-level ordinal stage variable, where stage 1 represents localised stage cancer and stage 4 indicates metastatic stage cancer (Benitez-Majano *et al*, 2016).

HES records were used to supplement treatment information gathered from the clinical audit data and to derive information on comorbidity prevalence. We devised an algorithm to derive the first major surgical treatment received by each patient within a time window of between 30 days prior and 90 days following cancer diagnosis. Treatment information was derived from data coded according to the Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures (fourth version, 'OPCS-4') (Health and Social Care Information Centre, 2017). The OPCS-4 codes represent an information standard used by clinical coders within National Health Service hospitals in Great Britain. In the clinical audit data, we used the sole OPCS-4-coded treatment variable describing the patient's primary procedure. In HES up to 12 fields (among a total of 20) capturing OPCS-4-coded treatment information had been completed for each hospital episode. Major surgery was categorised using the definition of major treatment devised by the Site-Specific Clinical Reference Groups of the National Cancer Intelligence Network (National Cancer Intelligence Network, 2013), which sought extensive input from clinicians and oncologists. Supplementary Table 1 defines OPCS-4 codes representing major surgery for colon cancer. Surgery presentation was defined as either 'emergency' or 'elective', according to the method of admission recorded in HES.

Information on the presence of comorbidities and other conditions were derived from the historical records of diagnosis fields in HES between 2003 and 2013, allowing the capture of information up to 6.5 years prior to cancer diagnosis. Each hospital spell record can contain up to 20 diagnostic fields in which coexisting conditions could be recorded. We extracted information on the prevalence of the 17 comorbidities of the Charlson Index (Charlson *et al*, 1987) plus obesity by applying an algorithm (Maringe *et al*, 2017) that created a binary variable to flag the presence of each of the comorbidities of interest prior to the date of cancer diagnosis recorded in the registry data. We considered comorbidities recorded during a retrospective 6-year period from 0.5 to 6.5 years prior to cancer diagnosis in the analysis. Cancer registry data were the source of information for the two Charlson Index comorbidities relating to cancer (i.e., 'any malignancy' and 'metastatic solid tumours'). However, stage information was largely missing for many cancers and, where available, we found only 11 colon cancer patients with a metastatic tumour (i.e., TNM stage 4 tumour) prior to the diagnosis of their colon cancer. We therefore considered any prior cancer diagnosis as 'any malignancy' in the context of the Charlson Index. Each patient's Charlson Comorbidity Index score was calculated based on Charlson's weighted index of comorbidity (Charlson *et al*, 1987). A weighted score was derived for each patient based on whether any of the comorbidities had been diagnosed, as confirmed from the binary comorbidity indicators. The Charlson Comorbidity Index scores were then summarised by creating a four-category comorbidity score variable, indicating whether the Charlson Comorbidity Index score was 0, 1, 2 or $\geqslant 3$.

We defined socio-economic status as deprivation, which was measured using the Income Domain from the 2011 England Indices of Multiple Deprivation (Department for Communities and Local Government, 2011) defined at the Lower Super Output Area level (mean population 1500). Patients were allocated to one of the five deprivation categories according to their area of residence at the time of their cancer diagnosis. This ecological, five-level ordinal variable represents a scale of deprivation, where '1' represents the least deprived and '5' represents the most deprived category of patients, based on the quintiles of the distribution areas in England.

Analysis. All analyses were conducted using Stata 14 (StatCorp LP, College Station, TX, USA) (StataCorp, 2015).

Information on patient characteristics was investigated using cross tabulations to explore the distribution and completeness of variables of interest for each gender.

The first step was to quantify the role of key variables on the 90-day mortality, which then enabled us to derive a series of indicators with public health relevance, discussed in the next subsection. Prior to conducting our analyses, the relationships between the prognostic factors (age, stage at diagnosis, treatment received and comorbidity score), our primary exposure of interest (deprivation) and the outcome of interest (90-day mortality) were considered. A directed acyclic graph depicting the assumed relationships between these variables is provided in Supplementary Figure 1.

We used multivariable logistic regression models to estimate the associations between the probability of death occurring within 90 days of colon cancer diagnosis (our outcome of interest) and deprivation as well as age at diagnosis, stage at diagnosis, comorbidity score and treatment received, separately for each gender. The possible nonlinear effect of age at diagnosis was

modelled using a quadratic regression spline with one knot at 70 years (near the mean age of the patients, 72.2 years). Furthermore, because the association between deprivation and 90-day mortality might vary by stage, comorbidity and treatment, the initial multiple logistic regression model included, in addition to the variables mentioned above, the corresponding interactions. Similarly, interactions between stage and age, stage and treatment, stage and comorbidity and comorbidity and treatment were initially considered on *a priori* clinical grounds. A backward elimination method (Agresti, 2013) was then applied to select the most parsimonious model to predict 90-day mortality. This final analysis model was used to predict our outcome – probability of death within 90 days of diagnosis. As a further step, to examine the contribution stage and treatment made towards this outcome, we performed additional analysis removing in turn from our final analysis model, stage, treatment and both stage and treatment.

Multiple imputations accounted for 30% missing composite stage, assuming a missing at random mechanism (Little and Rubin, 1987) – that is, that the probability of stage being missing depended on the observed data. Given that the logistic regression model included (i) interactions between stage and other variables (and stage had missing information), and (ii) a nonlinear effect of age, multiple imputation by the substantive-model compatible fully conditional specification (SMC–FCS) method (Bartlett *et al*, 2015; Bartlett and Morris, 2015) was employed to ensure compatibility between the imputation model and the analysis model (Carpenter and Kenward, 2013). Separately for each gender, a multinomial logistic regression model was used to impute stage, including as predictor variables, (i) all the variables in the analysis model mentioned above, (ii) the vital status within 90 days, (iii) the tumour grade (a four-level ordinal variable indicating the level of differentiation of the tumour), and (iv) a variable representing the Nelson–Aalen estimate (an estimator of the cumulative hazard of death) (Falcaro *et al*, 2015). In this model, age was also included as a nonlinear effect, to ensure compatibility (Carpenter and Kenward, 2013) with the analysis model. Tumour grade was used as an auxiliary variable in the imputation model, and as it also had missing information (20% missing grade), a multinomial logistic regression model was also used to impute it within the SMC–FCS framework. It is important to mention that ordinal logistic regression models, rather than multinomial logistic regression models, could be employed to impute stage and grade, provided that care is taken to test for the usually made proportional odds assumption (Agresti, 2013; Carpenter and Kenward, 2013).

The Stata 'smcfcs' command (StataCorp, 2015) was used to generate 30 imputed data sets, using the imputation model and imputation strategy above. The initial multiple logistic regression model was fitted to the 30 imputed data sets and Rubin's Rules (Little and Rubin, 1987) used to combine the analysis results. The backward elimination model selection method was applied using the 'mi test' command (StataCorp, 2015) to perform a multivariate Wald test, dropping the most insignificant interaction term one at a time; refitting the reduced model to the data imputed as above and testing again for the remaining interactions, until all remaining interactions were significant (P-value $\leqslant 0.05$). All interactions were tested on the same set of imputed data: retaining the data imputed using the most complex imputation model and testing all subsequent reduced models on these same set of data ensures valid estimation of all the reduced models (Carpenter and Kenward, 2013; Bartlett and Morris, 2015).

Indicators produced. Using the final model selected for each gender, we predicted two sets of probabilities of dying within 90 days of diagnosis. The first consisted of conditional probabilities, that is, given specific values of the prognostic factors. This was performed using the 'mi estimate' command (StataCorp, 2015). The second set included average predicted probabilities estimated for each deprivation group in turn; we predicted the probability of death within 90 days of diagnosis for each patient, adjusting for prognostic factors, and averaged these probabilities on all patients in the subgroup (Muller and Maclehose, 2014). This meant the probability of death was predicted for each patient in the deprivation group – adjusting for the patient's prognostic factor values – and used to derive the average predicted probability of death of all patients in that deprivation group. By way of comparison, the average predicted probabilities were then recalculated separately for each of the deprivation groups but setting the level of deprivation as the least deprived group and with all other prognostic factors remaining as observed. This gave an estimate of the probability of death as if patients had been in the least deprived group. The difference between those two probabilities quantified the effect of deprivation. This was performed using the 'mimrgns' command. In the additional analysis, we reiterated this calculation of average predicted probabilities as if patients had been in the least deprived group but using the final model without stage, then without treatment and finally without both.

RESULTS

A total of 69 769 adults were diagnosed with colon cancer in England between January 2010 and March 2013; 36 685 (52.6%) of these adults were males. Table 1 shows the characteristics of the patients in this study overall and for the 14.7 and 16.6% males and females, respectively, who died within 90 days after a colon cancer diagnosis. As deprivation increased the percentage of patients in each deprivation group decreased in both genders (22.3 in deprivation group 1 *versus* 15.2% in deprivation group 5 in males and 21.4 *versus* 15.3% in females). However, by deprivation group, the percentage of patients who died in 90 days increased with deprivation: in the least deprived group, the percentage was 12.4 in males and 13.3% in females; and in the most deprived group, the percentages were 17.7 and 19.9 in males and females, respectively. Both male and female elderly patients were highly represented, especially the 80+ patients, in the patients who died within 90 days. Stage at diagnosis was missing for almost a third of the patients but for 38.1% and 44.3% of males and females who died within 90 days, respectively. Early stages (1 and 2) represented a third of the patients with observed stage but about 13% of those who died within 90 days. Only 74 males and 54 females diagnosed with stage 1 died within 90 days, compared with >2000 diagnosed with the most advanced stage 4 (representing three-quarters of the patients who did not survive). The patients with no recorded comorbidity were about three-quarters of all patients but were two-thirds of those who died within 90 days, illustrating an over-representation of those with no recorded comorbidity among the group who died within 90 days. About one-third of the patients did not receive any major surgery, but this group with no treatment represented over three-quarters of those who died within 90 days. By contrast, <10% of the patients who did not survive received a major elective surgery while they represented nearly half of all patients. We provide the distribution of stage at diagnosis in patients receiving a major emergency, major elective surgery or no major surgery in Supplementary Table 2. Of the 14 810 patients with known tumour stage who did not have a major surgery, 11.1% had a stage 1 diagnosis, whereas 66.6% had a stage 4 diagnosis. Supplementary Table 3 shows the distribution of patients who underwent major surgery via either emergency or elective presentation – and those who did not have major surgery – by comorbidity score. The majority of patients (51%) with the highest comorbidity score of 3 did not undergo major surgery while 34% of these patients had a major elective surgery. By contrast, 49% of patients with no

Table 1. Patient characteristics – patients diagnosed with colon cancer 2010–2013[a] in England

	Males				Females			
	Total		Died within 90 days		Total		Died within 90 days	
	N	%	*n*	%[b]	*N*	%	*n*	%[b]
Deprivation (Income Indices of Multiple Deprivation)								
Least deprived (1)	8180	22.3	1018	18.9	7078	21.4	946	17.2
2	8231	22.4	1124	20.9	7241	21.9	1109	20.2
3	7629	20.8	1114	20.7	7048	21.3	1195	21.8
4	7072	19.3	1132	21.1	6649	20.1	1232	22.4
Most deprived (5)	5573	15.2	989	18.4	5068	15.3	1006	18.3
Age (years)								
15–40	643	1.8	29	0.5	736	2.2	20	0.4
41–50	1182	3.2	68	1.3	1202	3.6	50	0.9
51–60	3386	9.2	283	5.3	2966	9.0	232	4.2
61–70	9889	27.0	840	15.6	7226	21.8	638	11.6
71–80	12 171	33.2	1674	31.1	9785	29.6	1333	24.3
81–99	9414	25.7	2483	46.2	11169	33.8	3215	58.6
Stage								
Missing	11 186	30.5[c]	2049	38.1[c]	10 531	31.8[c]	2430	44.3[c]
1 (localised)	3355	13.2[d]	74	2.2[d]	2647	11.7[d]	54	1.8[d]
2	7084	27.8[d]	368	11.1[d]	6571	29.1[d]	338	11.1[d]
3	6667	26.1[d]	388	11.7[d]	6006	26.6[d]	401	13.1[d]
4 (metastatic)	8393	32.9[d]	2498	75.1[d]	7329	32.5[d]	2265	74.1[d]
Comorbidity score								
0	26 314	71.7	3380	62.9	24 982	75.5	3600	65.6
1	3780	10.3	697	13.0	3552	10.7	772	14.1
2	3558	9.7	631	11.7	2521	7.6	542	9.9
3+	3033	8.3	669	12.4	2029	6.1	574	10.5
Treatment								
No major treatment	13 390	36.5	4056	75.4	11 811	35.7	4290	78.2
Major emergency treatment	5749	15.7	794	14.8	5962	18.0	868	15.8
Major elective treatment	17 546	47.8	527	9.8	15 311	46.3	330	6.0
Total	36 685	100.0	5377	14.7	33 084	100.0	5488	16.6

[a]2013 data represent diagnosis between 1 January 2013 and 31 March 2013.
[b]Representing the percentage of patients within each gender who died within 90 days.
[c]Representing the percentage of patients with missing stage information.
[d]Calculated as a percentage of patients with complete stage information.

recorded comorbidity had a major elective surgery and 33% no major surgery.

In building the multivariable model for obtaining the predictions of probability of death within 90 days, the model selection strategy identified significant interactions in both male and female patients, that is, the association between age and 90-day mortality was modified by stage, comorbidity and treatment. There was also an interaction between treatment and stage. In males only, one additional interaction was retained between comorbidity score and treatment.

Probability of death within 90 days of colon cancer diagnosis

Conditional probabilities by prognostic factor patterns. In both male and female patients, the conditional (i.e., conditional to specific values of factors) probability of death within 90 days rose with increasing level of deprivation, whatever the age and stage at diagnosis. To investigate this at a more granular level, the deprivation groups were split into subgroups of patients, according to the presence of comorbidities and the treatment they received. Therefore, for each sex, probability of death within 90 days was assessed in terms of each level of deprivation, age, stage, comorbidity score and treatment.

Table 2 presents the probability of death within 90 days for male and female patients in the most and least deprived patients, according to their age at diagnosis (60, 70 and 80 years), stage at diagnosis, comorbidity (no recorded comorbidity and the highest score of 3) and their treatment (major emergency surgery, major elective surgery or no major surgery). The most deprived patients were systematically more likely to die within 90 days than the least deprived patients, irrespective of age, stage, comorbidity and treatment status. For example, in males aged 70 years, with stage 2 diagnosis, comorbidity score 3 and who underwent a major emergency treatment, the probability of dying within 90 days was 11.7% (95% confidence interval (CI) 8.3, 16.3%) in the most deprived compared with 7.9% (95% CI 5.5, 11.2%) in the least deprived patients. Similarly, among those who underwent a major elective surgery, the probabilities of death were 3.8% (95% CI 2.7, 5.4%) and 2.5% (95% CI 1.7, 3.6%) in the most and least deprived, respectively. The probability of death varied by deprivation even among patients with no recorded comorbidity, regardless of their treatment. We observed very similar patterns in females.

By contrast, stage-2 patients with no recorded comorbidity experienced comparable 90-day mortality whether they had no major surgery or a major emergency surgery (Figure 1, Table 2). This was the case across all deprivation groups. For example, the probability of 90-day mortality among the most deprived female patients aged 70 years was 6.4% (95% CI 4.6, 8.8%) if not receiving any major surgery and 6.2% (95% CI 4.6, 8.3%) when receiving a major emergency surgery. These probabilities were much lower among females receiving a major elective surgery (1.0%, 95% CI 0.7, 1.6% with the same combination of factors). Among men only, the effect of comorbidity on the probability of 90-day mortality according to treatment differed: highest in those receiving

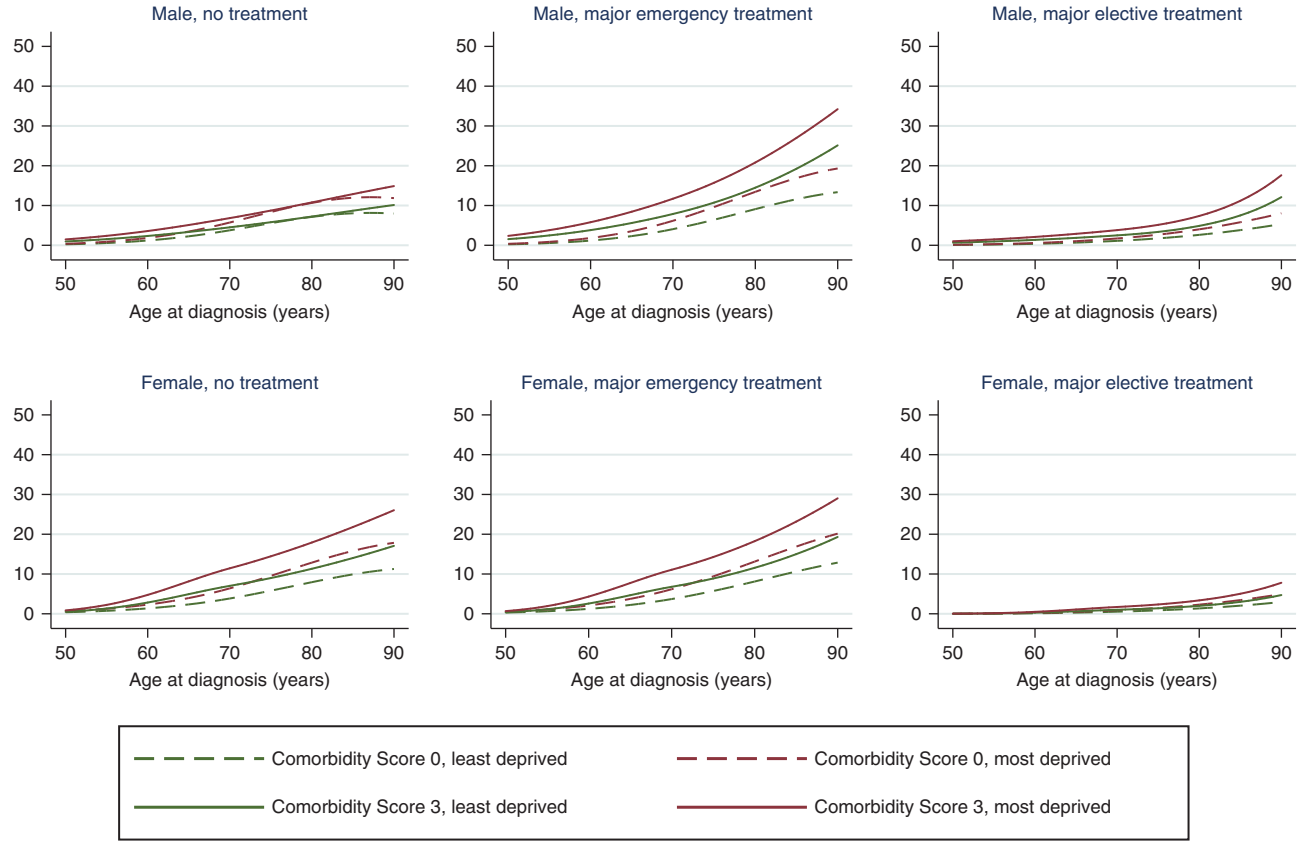

Figure 1. Probability (%) of death within 90 days of stage 2 colon cancer diagnosis according to age at diagnosis, among patients with (i) comorbidity score of 0 or 3 and (ii) from the least or the most deprived group.

emergency surgery, lowest in those receiving elective surgery, and intermediate in those with no surgery, regardless of their deprivation.

We provide graphs illustrating probability of death within 90 days of colon cancer diagnosis against age at diagnosis for each treatment type in both males and females, at each of the four stages of diagnosis (Figure 1, Supplementary Figures 2–4). The graphs contrast probability of death in the most and least deprived groups in patients with no recorded comorbidities and those with the maximum comorbidity score of 3. The general pattern was that more deprived patients were associated with higher 90-day mortality, regardless of the combination of other prognostic factors. Figure 1 presents these probabilities for stage-2 patients.

Average predicted probabilities by deprivation. In both males and females, the average predicted probabilities of death within 90 days of diagnosis identified a clear gradient across the observed deprivation groups, highest among the most deprived patients and lowest among the least deprived patients (Table 3, second and fourth columns). The existence of a difference in the average predicted probability of death between the most deprived and least deprived patient groups can be termed a 'deprivation gap'. The largest deprivation gap was in females, with 6.5% fewer deaths predicted within 90 days for the least deprived group compared with the most deprived (least deprived: 13.4%, 95% CI 12.7, 14.0%; and most deprived: 19.9%, 95% CI 19.0, 20.7%). In males, this gap was 5.3% (least deprived: 12.4%, 95% CI 11.8, 13.1%; and most deprived: 17.7%, 95% CI 16.9, 18.6%).

To explore the deprivation gap further, the probability of death was recalculated for each of the deprivation groups by predicting each group's probability of death as if it were the least deprived group, while all other prognostic factors remained as observed (Table 3, third and fifth columns). The results showed a shrinkage in the difference in probability of death between the most and least deprived groups, the difference became 1.7% and 1.3% in females and males, respectively. As expected, we observed the largest reduction in probability of death in the most deprived group: in females the reduction was 4.8% and in males the reduction was 4%.

In the additional analysis, when stage, treatment or both stage and treatment in combination were excluded from the final model and when the average predicted probability of death was calculated as if patients belonged to the least deprived group, there was a further reduction in the mortality difference between the most and least deprived patients from the one seen in the full analysis model (Supplementary Table 4). When stage alone was excluded from the model, the difference in probability of death between the most and least deprived patients reduced by approximately 30% (absolute difference of 0.9% compared with 1.3% with the final full model in males and 1.2% compared with 1.7% in females). For treatment alone, this percentage was 25% (absolute difference of 1% compared with 1.3% in males, and 1.3% compared with 1.7% in females). This suggested that, after accounting for the effect of deprivation, stage (or treatment) contributed to approximately one-third (or a quarter) of the remaining difference. When both stage and treatment were removed from the model, the remaining difference was close to 0%, indicating that in combination stage and treatment appear to contribute to most of the remaining difference in 90-day mortality once the effect of deprivation has been accounted for.

DISCUSSION

We found a very wide overall range of short-term mortality probabilities: for example, among female patients aged 60 years, those diagnosed with early stage colon cancer and who underwent

Table 2. Conditional probabilities of death within 90 days of colon cancer diagnosis

			Male			Female		
			Age at diagnosis, years			Age at diagnosis, years		
			60	70	80	60	70	80
	Comorbidity score	Deprivation group	PoD (%) (95% CI)	PoD (%) (95% CI)	PoD (%) (95% CI)	PoD (%) (95% CI)	PoD (%) (95% CI)	PoD (%) (95% CI)
Stage 1								
No major treatment	0	Least	0.2 (0.1; 0.6)	0.7 (0.4; 1.3)	1.9 (1.2; 2.9)	1.4 (0.8; 2.3)	3.8 (2.7; 5.4)	8.0 (6.2; 10.2)
		Most	0.4 (0.1; 1.0)	1.1 (0.7; 2.0)	2.9 (1.8; 4.5)	2.3 (1.4; 3.9)	6.4 (4.6; 8.8)	12.9 (10.1; 16.2)
	3	Least	0.5 (0.2; 1.3)	0.9 (0.5; 1.6)	1.9 (1.2; 3.0)	2.8 (1.5; 5.5)	7.0 (4.7; 10.3)	11.3 (8.5; 14.9)
		Most	0.7 (0.3; 2.0)	1.4 (0.8; 2.4)	2.9 (1.8; 4.6)	4.8 (2.5; 9.0)	11.4 (7.8; 16.4)	17.9 (13.8; 22.9)
Major emergency treatment	0	Least	0.3 (0.1; 1.4)	1.2 (0.4; 3.8)	3.6 (1.2; 10.4)	1.2 (0.7; 2.1)	3.7 (2.7; 5.0)	8.1 (6.5; 10.0)
		Most	0.5 (0.1; 2.2)	1.8 (0.6; 5.8)	5.4 (1.8; 15.2)	2.1 (1.3; 3.5)	6.2 (4.6; 8.3)	13.1 (10.7; 16.0)
	3	Least	1.1 (0.3; 4.7)	2.4 (0.7; 7.6)	5.9 (1.9; 16.6)	2.6 (1.4; 4.9)	6.8 (4.7; 9.7)	11.6 (9.0; 14.8)
		Most	1.7 (0.4; 7.1)	3.6 (1.1; 11.3)	8.9 (3.0; 23.7)	4.3 (2.3; 8.0)	11.1 (7.8; 15.4)	18.3 (14.5; 22.8)
Major elective treatment	0	Least	0.2 (0.1; 0.5)	0.5 (0.3; 0.8)	1.5 (1.0; 2.3)	0.1 (0.1; 0.3)	0.5 (0.4; 0.8)	1.4 (1.0; 1.8)
		Most	0.3 (0.1; 0.7)	0.8 (0.5; 1.3)	2.4 (1.6; 3.5)	0.2 (0.1; 0.4)	0.9 (0.6; 1.3)	2.3 (1.8; 3.0)
	3	Least	0.6 (0.2; 1.8)	1.1 (0.6; 1.9)	2.9 (1.8; 4.5)	0.3 (0.1; 0.6)	1.0 (0.7; 1.6)	2.0 (1.5; 2.7)
		Most	1.0 (0.3; 2.7)	1.7 (1.0; 3.0)	4.4 (2.8; 6.7)	0.5 (0.2; 1.0)	1.7 (1.1; 2.6)	3.4 (2.5; 4.6)
Stage 2								
No major treatment	0	Least	1.2 (0.7; 1.9)	3.8 (2.8; 5.1)	7.1 (5.5; 9.3)	1.4 (0.8; 2.3)	3.8 (2.7; 5.4)	8.0 (6.2; 10.2)
		Most	1.9 (1.2; 3.0)	5.7 (4.2; 7.7)	10.7 (8.2; 13.8)	2.3 (1.4; 3.9)	6.4 (4.6; 8.8)	12.9 (10.1; 16.2)
	3	Least	2.3 (1.3; 4.1)	4.5 (3.2; 6.4)	7.2 (5.4; 9.7)	2.8 (1.5; 5.5)	7.0 (4.7; 10.3)	11.3 (8.5; 14.9)
		Most	3.6 (2.1; 6.1)	6.8 (4.9; 9.5)	10.8 (8.1; 14.2)	4.8 (2.5; 9.0)	11.4 (7.8; 16.4)	17.9 (13.8; 22.9)
Major emergency treatment	0	Least	1.2 (0.7; 1.9)	4.1 (3.1; 5.3)	9.1 (7.3; 11.2)	1.2 (0.7; 2.1)	3.7 (2.7; 5.0)	8.1 (6.5; 10.0)
		Most	1.8 (1.2; 2.9)	6.2 (4.7; 8.0)	13.4 (10.9; 16.4)	2.1 (1.3; 3.5)	6.2 (4.6; 8.3)	13.1 (10.7; 16.0)
	3	Least	3.8 (2.1; 6.7)	7.9 (5.5; 11.2)	14.5 (10.8; 19.1)	2.6 (1.4; 4.9)	6.8 (4.7; 9.7)	11.6 (9.0; 14.8)
		Most	5.8 (3.3; 10.0)	11.7 (8.3; 16.3)	20.8 (15.9; 26.8)	4.3 (2.3; 8.0)	11.1 (7.8; 15.4)	18.3 (14.5; 22.8)
Major elective treatment	0	Least	0.4 (0.2; 0.6)	1.1 (0.9; 1.4)	2.6 (2.1; 3.2)	0.1 (0.1; 0.3)	0.5 (0.4; 0.8)	1.4 (1.0; 1.8)
		Most	0.6 (0.4; 0.9)	1.7 (1.3; 2.2)	4.0 (3.2; 5.0)	0.2 (0.1; 0.4)	0.9 (0.6; 1.3)	2.3 (1.8; 3.0)
	3	Least	1.4 (0.8; 2.4)	2.5 (1.7; 3.6)	4.9 (3.6; 6.6)	0.3 (0.1; 0.6)	1.0 (0.7; 1.6)	2.0 (1.5; 2.7)
		Most	2.1 (1.2; 3.7)	3.8 (2.7; 5.4)	7.4 (5.5; 9.9)	0.5 (0.2; 1.0)	1.7 (1.1; 2.6)	3.4 (2.5; 4.6)
Stage 3								
No major treatment	0	Least	3.2 (2.3; 4.5)	5.8 (4.6; 7.3)	9.8 (7.9; 12.1)	2.6 (1.7; 3.8)	4.7 (3.5; 6.2)	7.3 (5.8; 9.3)
		Most	4.9 (3.5; 6.9)	8.8 (6.9; 11.0)	14.5 (11.8; 17.7)	4.3 (2.9; 6.4)	7.7 (5.8; 10.2)	11.9 (9.4; 14.9)
	3	Least	6.1 (3.9; 9.4)	6.9 (5.2; 9.2)	9.9 (7.7; 12.7)	5.2 (3.0; 9.0)	8.5 (6.0; 11.9)	10.5 (8.0; 13.5)
		Most	9.2 (6.0; 13.8)	10.4 (7.9; 13.5)	14.6 (11.5; 18.4)	8.6 (5.1; 14.4)	13.7 (9.9; 18.7)	16.6 (13.0; 21.1)
Major emergency treatment	0	Least	2.0 (1.4; 2.9)	4.0 (3.1; 5.1)	8.1 (6.5; 10.1)	3.0 (2.1; 4.2)	5.7 (4.6; 7.2)	9.4 (7.8; 11.4)
		Most	3.1 (2.2; 4.4)	6.1 (4.8; 7.6)	12.0 (9.7; 14.8)	5.0 (3.5; 7.0)	9.4 (7.5; 11.7)	15.1 (12.5; 18.0)
	3	Least	6.3 (3.9; 10.1)	7.7 (5.5; 10.7)	13.0 (9.7; 17.3)	6.1 (3.6; 10.0)	10.3 (7.6; 13.9)	13.3 (10.5; 16.7)
		Most	9.4 (5.9; 14.8)	11.5 (8.3; 15.7)	18.8 (14.3; 24.4)	9.9 (6.0; 16.0)	16.4 (12.3; 21.5)	20.8 (16.8; 25.4)
Major elective treatment	0	Least	0.5 (0.4; 0.8)	0.9 (0.7; 1.2)	2.0 (1.5; 2.6)	0.3 (0.2; 0.6)	0.9 (0.6; 1.2)	1.6 (1.3; 2.2)
		Most	0.8 (0.6; 1.2)	1.4 (1.1; 1.9)	3.1 (2.4; 4.0)	0.6 (0.4; 0.9)	1.5 (1.1; 2.0)	2.8 (2.1; 3.7)
	3	Least	2.0 (1.2; 3.3)	2.1 (1.5; 3.0)	3.7 (2.6; 5.2)	0.7 (0.4; 1.4)	1.6 (1.1; 2.4)	2.4 (1.8; 3.3)
		Most	3.0 (1.8; 5.0)	3.2 (2.2; 4.6)	5.7 (4.1; 7.9)	1.2 (0.6; 2.3)	2.8 (1.9; 4.0)	4.1 (3.0; 5.5)
Stage 4								
No major treatment	0	Least	24.9 (22.7; 27.2)	33.2 (31.0; 35.4)	46.0 (43.4; 48.7)	24.4 (22.0; 27.0)	34.2 (31.8; 36.7)	49.1 (46.3; 51.9)
		Most	33.9 (31.2; 36.8)	43.5 (40.9; 46.1)	57.0 (54.2; 59.7)	35.6 (32.4; 38.9)	47.1 (44.2; 49.9)	62.3 (59.4; 65.0)
	3	Least	39.4 (31.6; 47.7)	37.5 (32.6; 42.6)	46.3 (41.8; 50.9)	40.5 (30.3; 51.6)	49.5 (42.9; 56.2)	58.8 (53.8; 63.6)
		Most	50.2 (41.8; 58.6)	48.2 (42.9; 53.4)	57.3 (52.7; 61.7)	53.8 (42.7; 64.5)	62.7 (56.3; 68.7)	70.9 (66.6; 74.9)
Major emergency treatment	0	Least	11.9 (9.8; 14.4)	18.1 (15.9; 20.6)	31.4 (27.9; 35.2)	11.1 (9.0; 13.6)	17.6 (15.3; 20.1)	29.6 (26.2; 33.2)
		Most	17.3 (14.5; 20.6)	25.6 (22.7; 28.7)	41.6 (37.3; 45.9)	17.5 (14.4; 21.2)	26.7 (23.5; 30.2)	41.8 (37.6; 46.1)
	3	Least	30.7 (22.1; 40.9)	30.9 (24.4; 38.2)	43.7 (36.3; 51.4)	20.8 (13.9; 29.9)	28.7 (23.0; 35.2)	38.3 (32.8; 44.1)
		Most	40.8 (30.6; 51.8)	41.0 (33.4; 48.9)	54.6 (46.9; 62.2)	31.0 (21.7; 42.1)	40.8 (33.9; 48.0)	51.5 (45.5; 57.5)
Major elective treatment	0	Least	3.8 (2.9; 5.0)	5.3 (4.4; 6.4)	10.4 (8.6; 12.6)	1.9 (1.3; 2.8)	4.1 (3.2; 5.2)	8.5 (6.9; 10.5)
		Most	5.8 (4.4; 7.5)	7.9 (6.6; 9.5)	15.3 (12.7; 18.3)	3.2 (2.2; 4.6)	6.8 (5.3; 8.5)	13.7 (11.2; 16.7)
	3	Least	12.7 (8.3; 19.0)	11.2 (8.2; 15.1)	18.1 (13.8; 23.4)	3.9 (2.2; 6.7)	7.4 (5.4; 10.2)	12.1 (9.4; 15.5)
		Most	18.5 (12.4; 26.6)	16.4 (12.3; 21.5)	25.6 (19.9; 32.2)	6.5 (3.7; 11.0)	12.1 (8.8; 16.2)	19.0 (15.0; 23.8)

Abbreviations: CI = confidence interval; PoD = probability of death.

a major elective surgery had a 90-day mortality probability near 0%, compared with a probability between 25% and 55% (depending on their deprivation group and comorbidity) for those with a stage-4 diagnosis who did not receive a major surgery. Deprivation differences in 90-day mortality were seen despite adjusting for major prognostic factors.

In our patient population, when calculating the average predicted probability of death within 90 days by deprivation group, and assuming that patients belong to the least deprived group, the differences between the probability of death in the least deprived group and the other deprivation groups became smaller. It translated to a total of 209 fewer deaths within 90 days of diagnosis per year in females and 168 fewer deaths per year in males (about 4% of the number of deaths observed in deprivation groups 2–5). Furthermore, when considering only the most deprived group of patients, it equated to approximately 74 and

Table 3. Average predicted probability of death within 90 days of colon cancer diagnosis: by deprivation

	Males		Females	
Deprivation group	Average predicted probability[a] (95% CI)	Average predicted probability, adjusted as if patients belonged to the deprivation group 1[b] (95% CI)	Average predicted probability[a] (95% CI)	Average predicted probability, adjusted as if patients belonged to the deprivation group 1[b] (95% CI)
Least deprived (1)	12.4 (11.8; 13.1)	12.4 (11.8; 13.1)	13.4 (12.7; 14.0)	13.4 (12.7; 14.0)
2	13.7 (13.0; 14.3)	12.9 (12.2; 13.5)	15.3 (14.7; 16.0)	14.1 (13.4; 14.8)
3	14.6 (13.9; 15.3)	13.3 (12.6; 14.0)	17.0 (16.3; 17.6)	14.8 (14.0; 15.5)
4	16.0 (15.3; 16.7)	13.6 (13.0; 14.3)	18.5 (17.8; 19.3)	15.5 (14.7; 16.2)
Most deprived (5)	17.7 (16.9; 18.6)	13.7 (13.0; 14.3)	19.9 (19.0; 20.7)	15.1 (14.4; 15.9)

Abbreviation: CI = confidence interval.
[a]Probability predicted for each deprivation group based on the observed value of the deprivation group, with the distribution of all prognostic factors remaining as observed.
[b]Probability predicted for each deprivation group adjusted to assume patients in each group belong to the least deprived group (group 1), with the distribution of all prognostic factors remaining as observed.

69 fewer deaths in females and males, respectively. These results suggested that the differential distribution of the prognostic factors in deprivation groups may account for some of the outcome differences observed.

In the additional analysis, when we explored the role stage and treatment may be having in 90-day mortality differences between the most and least deprived patients, we found that stage and treatment appeared to contribute towards almost all of the remaining difference between the most and least deprived patient groups. When the average predicted probability of death was calculated assuming all patients were in the least deprived group and after removing both stage and treatment from the model, the average predicted probabilities were almost the same between the most and least deprived patient groups.

Differential access of treatment by deprivation may explain some of the inequalities in mortality. The percentage of colon cancer cases diagnosed during an emergency admission was as high as 31.4% in England for diagnoses made between 2006 and 2010 (Abel *et al*, 2015). In Scotland, the most deprived patients were more likely to present as an emergency and undergo palliative surgery (Oliphant *et al*, 2013). The same study also found higher postoperative mortality among more deprived colorectal patients, after adjusting for comorbidity and stage. These findings are in line with ours, where the socio-economic differences in 90-day mortality were evident in both nonoperative and postoperative colon cancer patients. Comorbidity and stage provide some contribution towards differences in short-term cancer mortality, but the socio-economic inequalities in 90-day mortality probability persisted even within any given treatment category, after controlling for stage and comorbidity. In the context of randomised clinical trials, where stage, comorbidity and also treatment are well controlled, we did not find evidence of a deprivation gap in 1-year colorectal cancer survival (Nur *et al*, 2008).

In a broader context, other work discussed differences in the quality of postoperative care and availability of beds in high dependence and intensive care units in the institution where treatment is received as potential factors influencing short-term postoperative mortality (Morris *et al*, 2011). This is especially pertinent in the presence of a high prevalence of postoperative complications. Previous research in Australia found that patients from higher socio-economic areas had a lower risk of developing postoperative complications (Beckmann *et al*, 2016), reinforcing the need for adequate postoperative care facilities in the most deprived areas. Comparing postoperative care resourcing between institutions in more and lesser deprived areas could provide some explanation behind socio-economic differences in 90-day colon cancer mortality and should be examined in more detail. Our study included surgical treatment received up to 90 days after diagnosis but did not account for the time to surgical treatment. Other research has shown more deprived patients were more likely to receive late treatment, that is, later than a month since diagnosis (Lejeune *et al*, 2010).

The results of this study provided some insight into an existing dynamic between treatment, comorbidity and short-term mortality. This relationship has some complexity, as comorbidity affects survival and influences cancer management (Faivre *et al*, 2007). This complexity is more pronounced in the elderly: the frequency of comorbidity is often higher in the elderly (Colorectal Cancer Collaborative Group, 2000), they tend to have more advanced disease stage (Dekker *et al*, 2011), and postoperative mortality increases with age (Morris *et al*, 2011). Additionally, patients undergoing emergency major surgery had a higher 90-day probability of death than patients who had received elective major treatment. This concurs with previous research indicating emergency surgery in comorbid patients to be a risk factor for short-term mortality in postoperative colon cancer patients (Gooiker *et al*, 2012).

Some challenges were faced when conducting analyses for this study, in particular owing to the use of population-based data. We employed a robust imputation strategy to mitigate the disadvantage of having missing information on stage (Bartlett *et al*, 2015). This approach allowed us to select the most parsimonious model as the final model to predict probability of death within 90 days, while taking proper account of the missing data. The overall probability of 90-day mortality was estimated as 14.7% (95% CI 14.4, 15.0%) for males and 16.6% (95% CI 16.3, 16.9%) for females. These predictions closely align with the observed proportion of deaths occurring within 90 days in our study population, confirming the goodness of fit of the analysis model on the observed data.

Information on treatment received by patients in our study was obtained using records from public hospitals. Some patients in our study may have received treatment in private facilities, which is not captured in our study. However, the proportion of cancer patients receiving surgical treatment outside the National Health Service has historically been small (Lawrence, 2013).

Our method for deriving patient comorbidity information was dependent on patients visiting the hospital and being diagnosed with the comorbidity in the time period of interest. We acknowledge the possibility that some comorbid adults may not have attended hospital nor had a comorbidity diagnosis recorded in this time, and therefore their comorbidity score would be 0. When available, including nonsurgical treatment in the analysis may provide additional insight into disparities in 90-day mortality between colon cancer patient groups, although surgery remains the primary curative treatment for colon cancer.

In conclusion, this study gives a full picture of 90-day probability of death according to the main prognostic factors and highlights persistent socio-economic inequalities in short-term mortality, even after accounting for the main prognostic factors,

including prediagnosis comorbidities that could be derived from hospital attendance records and cancer registry data. Indeed, these socio-economic differences in 90-day mortality were especially apparent in the older patients, as probability of 90-day mortality increased with age. The provision of treatment involves consideration as to whether patients can withstand the trauma of surgery, particularly where patients have comorbid conditions. This is especially true in older patients more vulnerable to the aftermath of surgery. The planning of cancer treatment and care would need to focus decisions to treat patients on patient performance status and comorbidities, rather than their chronological age (Lawler *et al*, 2014). Socio-economic inequalities in 90-day mortality being found even among non-vulnerable patients suggest that resources for optimal treatment planning and postoperative care facilities may not be equally accessible to all patient deprivation groups. This study has identified a need to focus on understanding what is driving the effect of deprivation on 90-day mortality, including differences in health-care-seeking behaviours. Based on the findings of this population-based study, beneficial health policy initiatives could include targeted screening programmes to facilitate earlier-stage diagnosis in vulnerable patient groups, improved preoperative planning, including evaluation of comorbid patients, and more stringent postoperative monitoring of the patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)

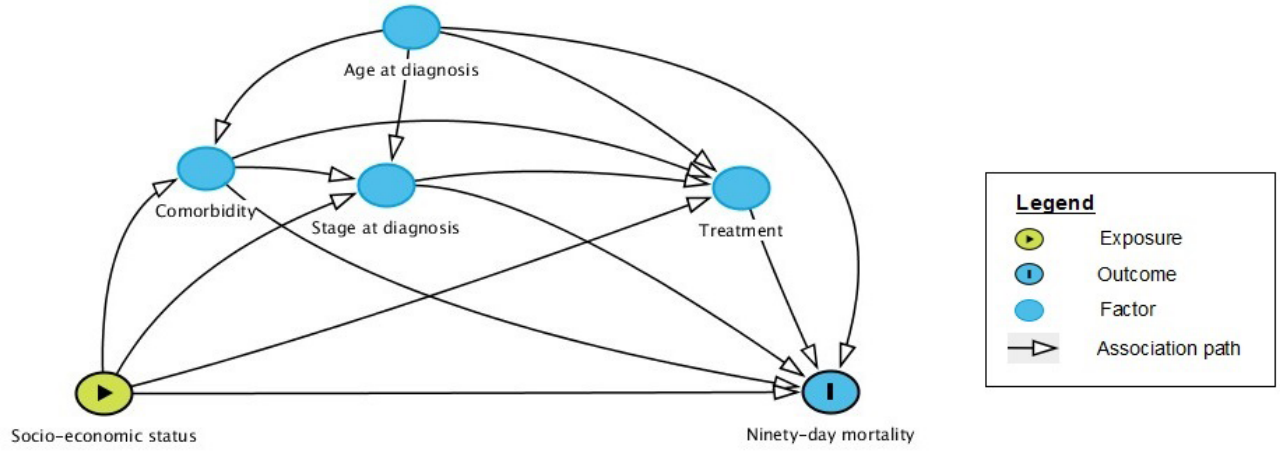
Supplementary Table 1: Major surgery, as defined using OPCS-4 codes

Code	Description
H011	Emergency excision of abnormal appendix and drainage HFQ
H012	Emergency excision of abnormal appendix NEC
H013	Emergency excision of normal appendix
H018	Other specified emergency excision of appendix
H019	Emergency appendicectomy NEC, unspecified
H021	Interval appendicectomy
H022	Planned delayed appendicectomy NEC
H023	Prophylactic appendicectomy NEC
H024	Incidental appendicectomy
H028	Other specified other excision of appendix
H029	Appendicectomy NEC, unspecified
H041	Proctocolectomy NEC, panproctocolectomy and ileostomy
H042	Panproctocolectomy and anastomosis of ileum to anus and creation of pouch HFQ
H043	Panproctocolectomy and anastomosis of ileum to anus NEC
H048	Other specified total excision of colon and rectum
H049	Panproctocolectomy NEC, total excision of colon and rectum, unspecified
H051	Total colectomy and anastomosis of ileum to rectum
H052	Total colectomy and ileostomy and creation of rectal fistula HFQ
H053	Total colectomy and ileostomy NEC
H058	Total excision of colon, other specified
H059	Total excision of colon, unspecified
H061	Extended right hemicolectomy and end to end anastomosis
H062	Extended right hemicolectomy and anastomosis of ileum to colon
H063	Extended right hemicolectomy and anastomosis NEC
H064	Extended right hemicolectomy and ileostomy HFQ
H068	Other specified extended excision of right hemicolon
H069	Extended excision of right hemicolon, unspecified, excision of right colon and surrounding tissue
H071	Right hemicolectomy and end to end anastomosis of ileum to colon, ileocaecal resection
H072	Right hemicolectomy and side to side anastomosis of ileum to transverse colon
H073	Right hemicolectomy and anastomosis NEC
H074	Right hemicolectomy and ileostomy HFQ
H078	Other specified other excision of right hemicolon
H079	Other excision of right hemicolon, unspecified; right hemicolectomy NEC
H081	Transverse colectomy and end to end anastomosis
H082	Transverse colectomy and anastomosis of ileum to colon
H083	Transverse colectomy and anastomosis NEC
H084	Transverse colectomy and ileostomy HFQ
H085	Transverse colectomy and exteriorisation of bowel NEC
H088	Other specified excision of transverse colon
H089	Excision of transverse colon, unspecified
H091	Left hemicolectomy and end to end anastomosis of colon to rectum
H092	Left hemicolectomy and end to end anastomosis of colon to colon
H093	Left hemicolectomy and anastomosis NEC
H094	Left hemicolectomy and ileostomy HFQ
H095	Left hemicolectomy and exteriorisation of bowel NEC
H098	Excision of left hemicolon, other specified
H099	Left hemicolectmy NEC, excision of left hemicolon, unspecified
H101	Sigmoid colectomy and end to end anastomosis of ileum to rectum
H102	Sigmoid colectomy and anastomosis of colon to rectum
H103	Sigmoid colectomy and anastomosis NEC
H104	Sigmoid colectomy and ileostomy HFQ
H105	Sigmoid colectomy and exteriorisation of bowel NEC
H108	Other specified excision of sigmoid colon
H109	Unspecified excision of sigmoid colon
H111	Colectomy and end to end anastomosis of colon to colon NEC
H112	Colectomy and side to side anastomosis of ileum to colon NEC
H113	Colectomy and anastomosis NEC
H114	Colectomy and ileostomy NEC
H115	Colectomy and exteriorisation of bowel
H118	Other excision of colon, other specified
H119	Hemicolectomy NEC; colectomy NEC, other excision of colon, unspecified
H121	Excision of diverticulum of colon
H122	Polypectomy NEC, excision of lesion NEC
H123	Destruction of lesion of colon NEC
H128	Other specified extirpation of lesion of colon
H129	Unspecified extirpation of lesion of colon
H291	Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus
H292	Subtotal excision of colon and rectum and creation of colonic pouch NEC

Code	Description
H293	Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum
H294	Subtotal excision of colon and creation of colonic pouch NEC
H298	Subtotal excision of colon, other specified
H299	Subtotal excision of colon, unspecified
H331	Abdominoperineal excision of rectum and end colostomy
H332	Proctectomy and anastomosis of colon to anus
H333	Anterior resection of rectum and anastomosis of colon to rectum using staples
H334	Anterior resection of rectum and anastomosis NEC
H335	Hartmann procedure, rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel
H336	Anterior resection of rectum and exteriorisation
H337	Perineal resection of rectum HFQ
H338	Anterior resection of rectum NEC, rectosigmoidectomy and anastomosis of colon to rectum, excision of rectum, other specified
H339	Rectosigmoidectomy NEC, excision of rectum, unspecified
H341	Open excision of lesion of rectum: open removal of polyp; Yorke Mason
H342	Open cauterisation of lesion of rectum, Diathermy
H343	Open cryotherapy to lesion of rectum
H344	Open laser destruction of lesion of rectum
H345	Open destruction of lesion of rectum NEC
H348	Open removal of lesion of rectum, other specified
H349	Open removal of lesion of rectum, unspecified
H401	Trans-sphincteric excision of mucosa of rectum
H402	Trans-sphincteric excision of lesion of rectum
H403	Trans-sphincteric destruction of lesion of rectum
H404	Trans-sphincteric anastomosis of colon to anus
H408	Other specified operations on rectum through anal sphincter
H409	Unspecified operations on rectum through anal sphincter
X141	Total exenteration of pelvis
X142	Anterior exenteration of pelvis
X143	Posterior exenteration of pelvis
X148	Other specified clearance of pelvis
X149	Clearance of pelvis, unspecified

Abbreviations: NEC, Not elsewhere specified; HFQ, however further qualified

Supplementary Figure 1: Directed acyclic graph showing the assumed relationships between the variables in our analysis



Supplementary Table 2: Distribution of stage at diagnosis by treatment received in patients diagnosed with colon cancer 2010-2013† in England								
	No major treatment		Major emergency treatment		Major elective treatment		TOTAL	
	n	%	n	%	n	%	n	%
Stage								
Total missing stage	10,391	*47.8**	3,344	*15.4**	7,982	*36.8**	**21,717**	***31.1***
1	1,649	*11.1***	287	*3.4***	4,066	*16.3***	**6,002**	***8.6***
2	1,472	*9.9***	2,609	*31.2***	9,574	*38.5***	**13,655**	***19.6***
3	1,828	*12.3***	2,831	*33.8***	8,014	*32.2***	**12,673**	***18.2***
4	9,861	*66.6***	2,640	*31.6***	3,221	*12.9***	**15,722**	***22.5***
TOTAL	**25,201**	***36.1***	**11,711**	***16.8***	**32,857**	***47.1***	**69,769**	***100.00***

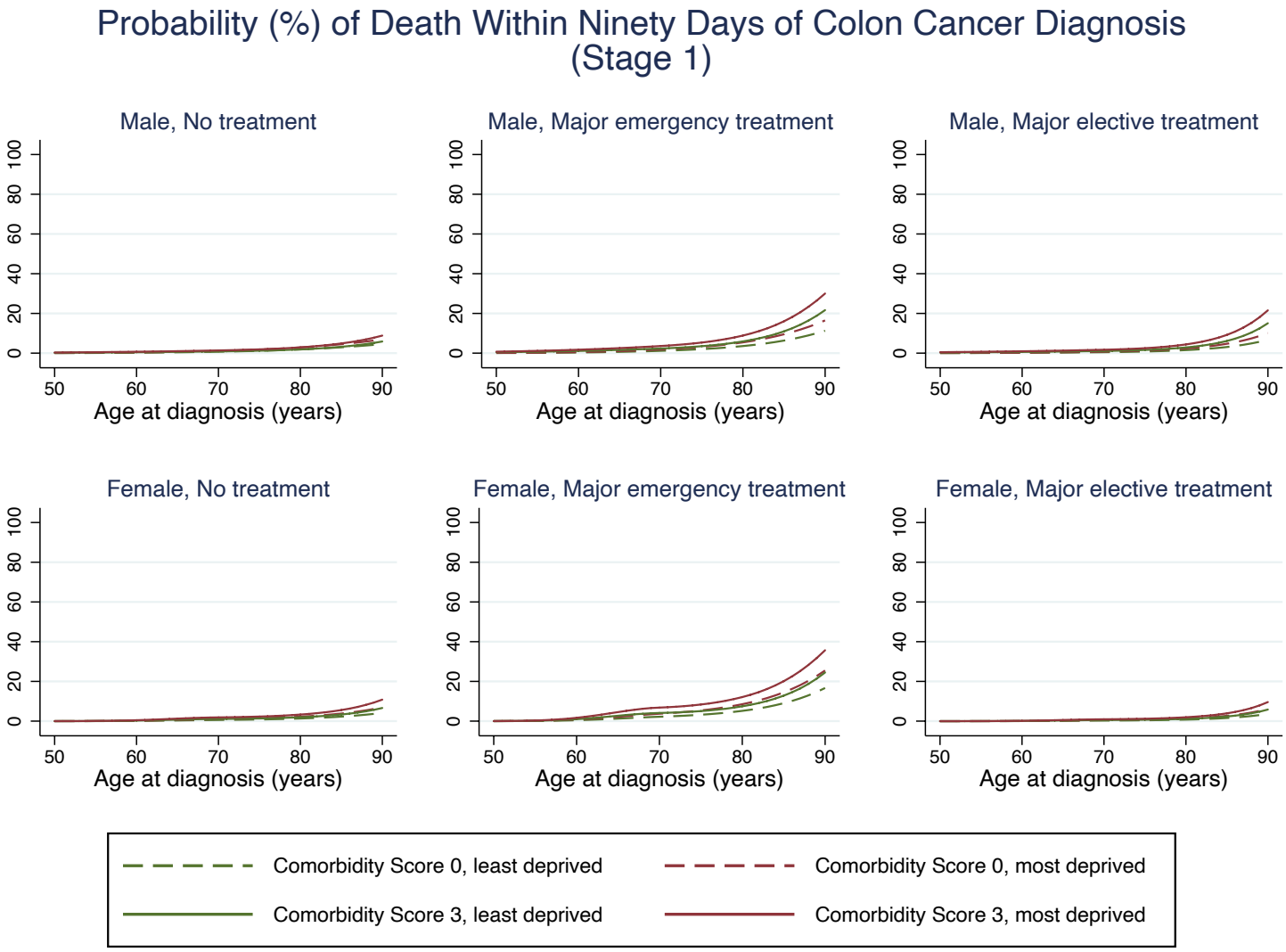
* Representing the proportion of all patients in this group

** Representing the proportion of patients with complete stage information in this group

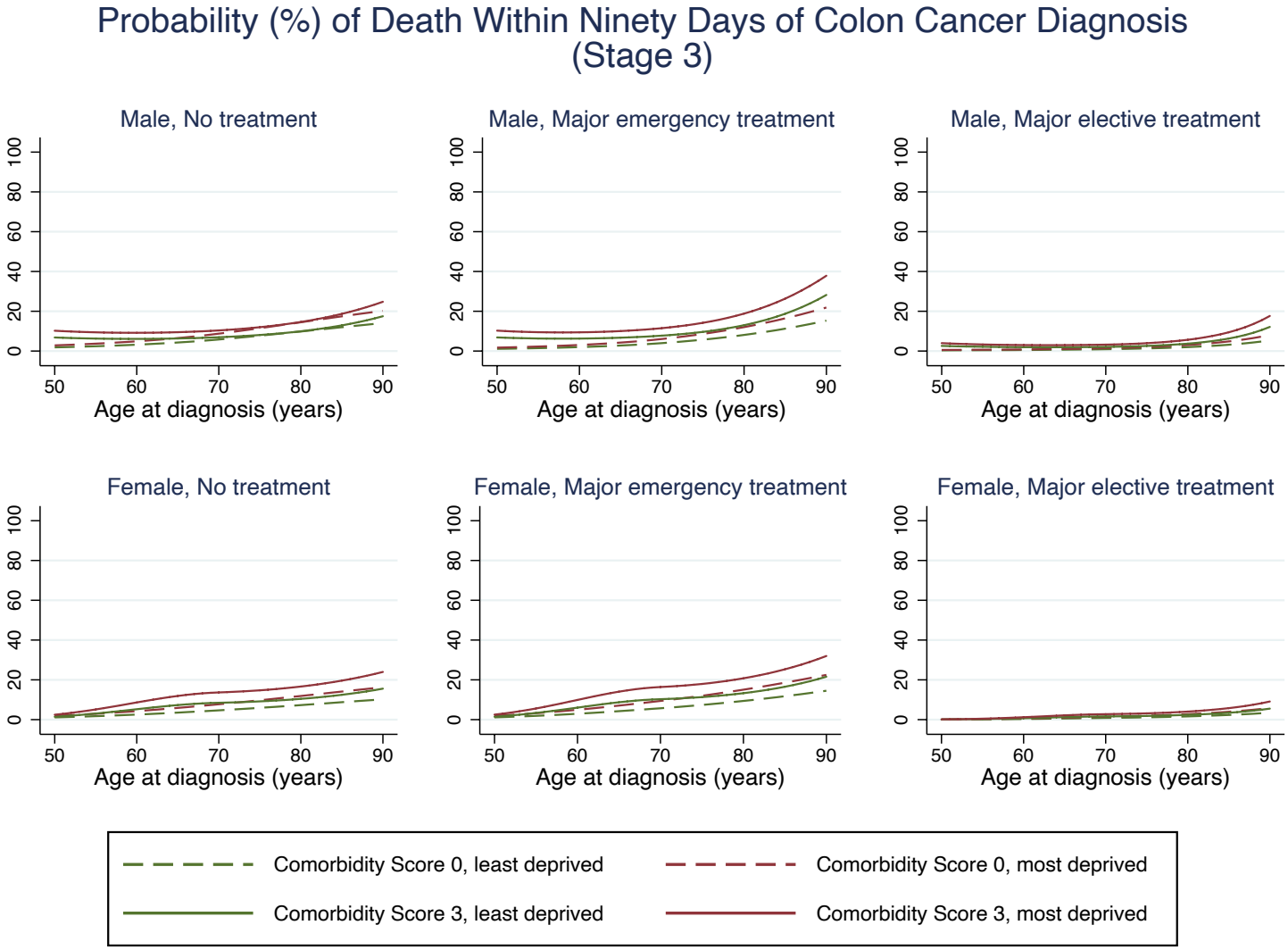
† 2013 data represents diagnosis between 1st January 2013 and 31st March 2013

Supplementary Table 3: Distribution of treatment received by comorbidity score in patients diagnosed with colon cancer 2010-2013† in England										
	Comorbidity Score									
	0		1		2		3		TOTAL	
	n	%	n	%	n	%	n	%	n	%
Treatment										
No major surgery	17,088	*33.3*	3,062	*41.8*	2,452	*40.3*	2,599	*51.3*	**25,201**	***36.12***
Major emergency surgery	8,979	*17.5*	1,151	*15.7*	859	*14.1*	722	*14.3*	**11,711**	***16.79***
Major elective surgery	25,229	*49.2*	3,119	*42.5*	2,768	*45.5*	1,741	*34.4*	**32,857**	***47.09***
TOTAL	**51,296**	***73.5***	**7,332**	***10.5***	**6,079**	***8.7***	**5,062**	***7.3***	**69,769**	***100.00***
† 2013 data represents diagnosis between 1st January 2013 and 31st March 2013										

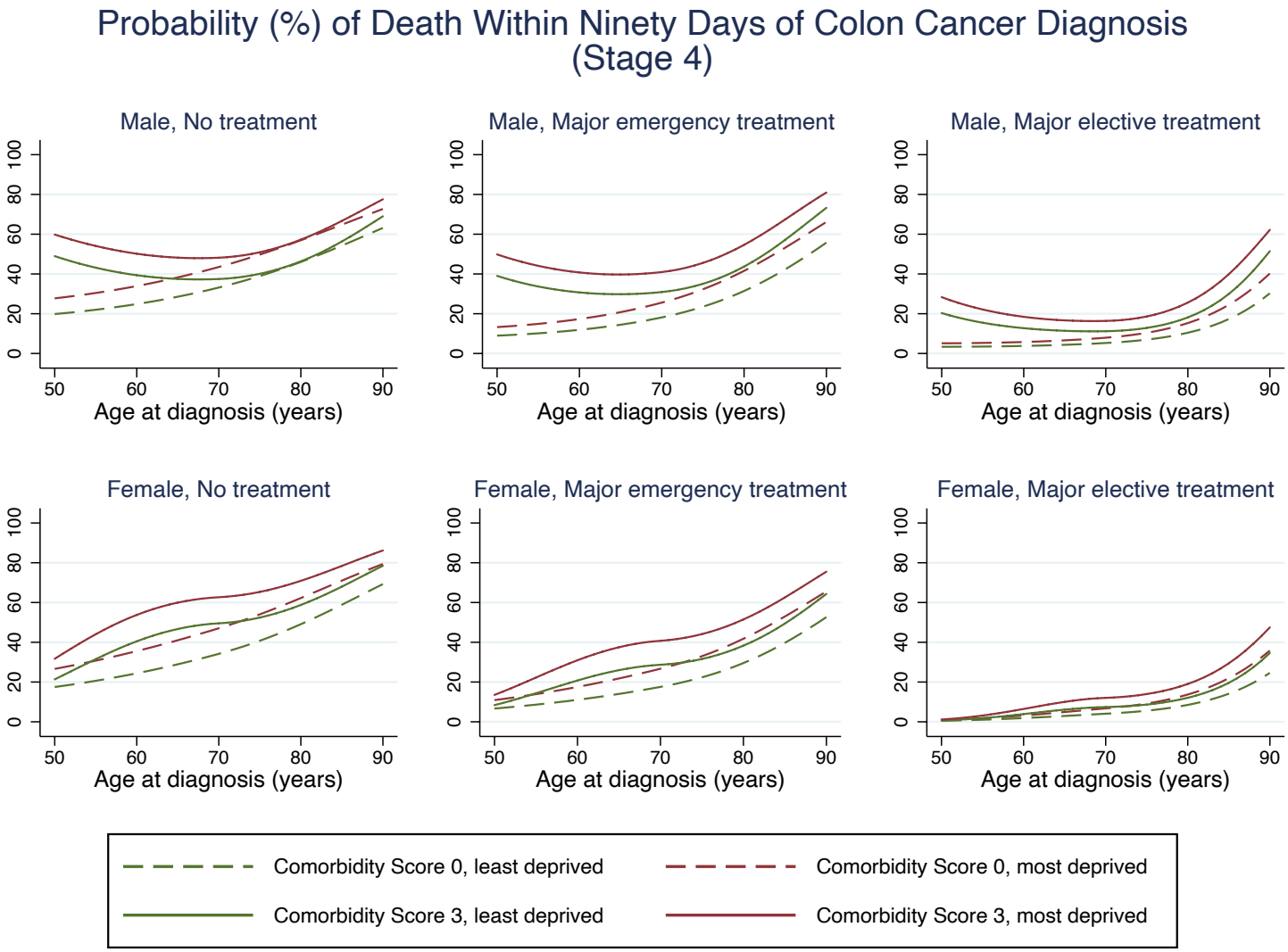
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Supplementary Table 4: Average predicted probability of death (%) within ninety days: by deprivation - additional analyses				
	Average predicted probability, adjusted as if patients belonged to deprivation group 1* [95% CI]			
Deprivation group	**Final analysis model**	**Model excludes stage**	**Model excludes treatment**	**Model excludes stage and treatment**
Males				
Least deprived (1)	12.4 [11.8; 13.1]	12.4 [11.8; 13.1]	12.4 [11.8; 13.1]	12.4 [11.7; 13.1]
2	12.9 [12.2; 13.5]	12.8 [12.1; 13.5]	12.8 [12.1; 13.5]	12.9 [12.2; 13.7]
3	13.3 [12.6; 14.0]	13.0 [12.3; 13.7]	13.2 [12.5; 13.9]	12.8 [12.1; 13.5]
4	13.6 [13.0; 14.3]	13.3 [12.6; 14.0]	13.4 [12.7; 14.1]	12.7 [11.9; 13.4]
Most deprived (5)	13.7 [13.0; 14.3]	13.3 [12.6; 14.0]	13.4 [12.7; 14.1]	12.5 [11.8; 13.2]
Females				
Least deprived (1)	13.4 [12.7; 14.0]	13.4 [12.7; 14.1]	13.4 [12.7; 14.0]	13.4 [12.6; 14.1]
2	14.1 [13.4; 14.8]	13.9 [13.2; 14.7]	14.1 [13.4; 14.9]	13.9 [13.1; 14.7]
3	14.8 [14.0; 15.5]	14.4 [13.7; 15.2]	14.8 [14.1; 15.6]	14.2 [13.4; 15.0]
4	15.5 [14.7; 16.2]	15.1 [14.3; 15.8]	15.4 [14.6; 16.2]	14.5 [13.7; 15.3]
Most deprived (5)	15.1 [14.4; 15.9]	14.6 [13.8; 15.4]	14.7 [13.9; 15.4]	13.7 [12.9; 14.5]

CI, confidence interval

* Probability predicted for each deprivation group adjusted to assume patients in each group belong to the least deprived group (group 1), with the distribution of all prognostic factors remaining as observed

Chapter 4 - Comorbidity prevalence among cancer patient populations

This chapter describes the research undertaken to achieve both parts of the second objective of this thesis: to i) describe and ii) evaluate the measurement of comorbidity prevalence in the cancer patient population. The research conducted for the first part of the objective resulted in a research paper which describes a population-based study of the prevalence of comorbidity among four cohorts of cancer patients. This paper was published in BMC Cancer in January 2020 and is referred to as research paper 2. The first section of this chapter provides the background, description, summary of main findings and conclusions of this descriptive study, together with a copy of the research paper.

The second section of the chapter explains the research conducted to address the second part of the objective: to evaluate the measurement of cancer comorbidity. This study examined sources of information on chronic disease prevalence in other cancer patient cohorts and in the general population. The background, methods, results and conclusions from this study have been written up in this chapter.

At the end of the chapter is a discussion of how this work fulfils the second objective and informs the research conducted in next chapter.

Introduction to research paper 2

Background

The presence of comorbidity can influence the care of cancer patients,[13, 105, 106] and is considered a prognostic factor in cancer outcomes.[87, 107-109] This has been highlighted in studies of colon or colorectal cancer patients,[48, 57, 110-112] including the study I conducted of ninety-day mortality among

colon cancer patients that was described the previous chapter of this thesis (**Research Paper 1**).[101] A study of cancer patients in the United States reported that patients with localised stage colon cancer and moderate or severe comorbidity (based on the Adult Comorbidity Evaluation Index (ACE-27)[113]) had almost 2.5 times the hazard of dying within one year of diagnosis as compared with colon cancer patients with localised stage and no comorbidity (HR 2.48; 95% CI: 1.67, 3.68).[110] Similarly, a study of colorectal cancer patients in the North West of England reported that patients with a Charlson comorbidity score of 3 or more had 1.8 times the hazard of death within one year, after adjusting for stage and other prognostic factors.[48] In the study of colon cancer patients described in Research Paper 1, those with a Charlson comorbidity score of 3 or more consistently had a higher probability of death than those without any recorded comorbidity, regardless of sex, age, stage at diagnosis, receipt of major surgery and deprivation group.[101]

Multimorbidity and comorbidity are associated with age[114, 115] but also with socio-economic position, with a greater burden of multimorbidity falling among the most deprived members of the population.[14, 15, 64] Moreover, the prevalence of various comorbid conditions among cancer patients is not very well known. A study in New Zealand investigated the prevalence of 50 conditions among 14,096 cancer patients, including 3,999 patients with cancer of the colon, based upon hospital admissions data. The most common conditions among the cohort of colon cancer patients included hypertension (17%), coagulopathy and blood disorders (12%), metabolic disorders (9%) and cardiac diseases (8%).[116] By comparison, a study of 1,061 colorectal cancer patients in two regions of Spain found common conditions to be diabetes (24%), chronic obstructive pulmonary disease (17%) and congestive heart failure (15%).[117] However, there is limited information available on the prevalence of comorbidity among cancer patients in England, or on how the prevalence of these conditions varies according to factors such as socio-economic deprivation. Further research to investigate patterns of comorbidity prevalence among cancer patients, particularly among the more deprived groups, may

help to increase our understanding of which groups of comorbid patients have a higher risk of dying soon after cancer diagnosis.

The first aim of this study was to estimate the prevalence of comorbid conditions among cancer patients in England using population-based electronic health records of hospital admissions. The second aim was to describe patterns of comorbidity according to patient characteristics, such as socio-economic position.

Description

This study examines comorbidity prevalence among patients diagnosed with cancer of the colon, rectum or lung, or with Hodgkin lymphoma in England between 2009 and 2013. [118, 119] The choice of these cancers was based on their aetiology. The development of colon, rectal or lung cancers is associated with environmental or lifestyle risk factors such as poor diet, excessive alcohol use and tobacco smoking.[120] The risk factors for these cancers are also associated with the development of other chronic diseases. For example, smoking is associated with developing chronic obstructive pulmonary disease,[121] while poor diet[122, 123] and smoking[124] increase the risk of developing diabetes. It was therefore anticipated that the prevalence of conditions such as these would be higher among patients with these cancers. As a contrast, Hodgkin lymphoma was studied as it tends to have an infectious rather than an environmental aetiology.[118] Prior exposure to the Epstein Barr virus has been shown to increase the risk of developing Hodgkin lymphoma.[118, 125] Additionally, the development of the other three cancers tends to be associated with older age,[126] while Hodgkin lymphoma has a bimodal age distribution, most commonly occurring in children and younger adults or in older adults.[125]

The study uses national cancer registry data linked with electronic health records of hospital visits, and investigates the prevalence of conditions recorded in these data up to six years prior to cancer diagnosis. Information on non-cancer comorbidities was extracted from hospital admissions records using an algorithm initially published in a research paper in PLoS One[76] and further described earlier in this thesis. Information on previous malignancies was obtained from cancer registration data. The choice of comorbid conditions to study followed a thorough exploration of these data to ascertain the prevalence of approximately fifty conditions. The fourteen selected conditions of interest were conditions of the Charlson Comorbidity Index[83] and other highly prevalent conditions that may influence cancer treatment or prognosis, either in isolation or in combination with other conditions.

The analyses conducted for this descriptive study firstly involved estimation of both the crude and age-sex prevalence of each of these conditions. Logistic regression was then used to estimate the odds of having each condition, adjusting for age, sex and deprivation, to look for associations between these variables and each of the comorbid conditions. Cross tabulations of the data provided relative frequencies in which five of the common conditions were present in combination with other conditions. Multinomial logistic regression was used to estimate the probability of having each condition as a single comorbidity or as one of multiple comorbidities, according to whether patients were in the most or the least deprived socio-economic deprivation groups.

Main findings

The findings from this study were reported in the research paper entitled "Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers" published in BMC Cancer in January 2020.[127] These findings were also presented at scientific conferences, listed in the Appendices to this thesis.

Among the four cohorts of cancer patients studied, up to two thirds of the lung cancer patients and approximately half the colon cancer patients (56%) and the rectal cancer patients (47%) had at least one long-term health condition when their cancer was diagnosed. Comorbidity was less prevalent among the cohort of patients with Hodgkin lymphoma (30%), which had a younger age demographic than the other cancers studied. The most prevalent comorbid conditions among all four cohorts of cancer patients studied were hypertension, chronic obstructive pulmonary disease (COPD) and diabetes. Among colon cancer patients the age-sex adjusted prevalence of these conditions was 17.4% (95%CI: 17.0%, 17.8%), 10.8% (10.2%, 11.3%) and 5.7% (5.4%, 5.9%) for hypertension, COPD and diabetes, respectively. Almost all of the conditions studied were associated with socio-economic deprivation, with increasing odds of the condition being present as deprivation level increased, after adjusting for age and sex. For example, the most deprived male colon cancer patients aged 70 years had twice the odds of having COPD (OR 2.01; 95%CI: 1.89, 2.12) and 75% increased odds (OR 1.75; 1.64, 1.87) of having diabetes compared with the least deprived group of male patients of the same age. To put these results into context, among the cohort of colon cancer patients the age-sex adjusted prevalence of COPD was approximately 11% (prevalence: 10.8%; 95% CI: 10.2%, 11.3%) and the adjusted prevalence of diabetes approximately 6% (prevalence 5.7%; 5.4%, 5.9%). The most prevalent of the conditions studied was hypertension, with an adjusted prevalence of 17% (17.4%; 17.0%, 17.8%) among the colon cancer patient cohort. Only 29% of the patients with COPD and 14% of the patients with diabetes had these conditions as a single comorbidity, while the prevalence of multiple comorbidity was commonly highest in the most deprived groups of patients. Among the colon cancer patient cohort, a difference between the most and least deprived groups in the probability of having hypertension, COPD and diabetes as one of multiple comorbidities was established even by the age of 45 years. This gap widened with increasing age. These patterns described among the colon cancer patient cohort were also observed among the other patient cohorts.

Conclusion

The study findings have illustrated sociodemographic factors influencing the presence of comorbidity among cancer patients. Over half of the colon cancer patient cohort studied had at least one comorbid condition and over one quarter had two or more comorbid conditions. This population-based study highlights an association between socio-economic deprivation and comorbidity among cancer patients in England. It also underlines the prevalence of multiple comorbidity, particularly among the most deprived groups.

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SECTION A – Student Details

Student	Helen Fowler
Principal Supervisor	Bernard Rachet
Thesis Title	The role of comorbidity in socioeconomic inequalities in short-term mortality among colon cancer patients in England

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMC Cancer		
When was the work published?	January 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of the paper. I conducted the literature review, designed the study and carried out the data analysis. I prepared all drafts of the paper. The coauthors provided input and feedback on some aspects of the analysis strategy and on the drafts of the paper that I had prepared.

Student Signature: [redacted] **Date:** 16/10/20

Supervisor Signature: [redacted] **Date:** 19 October 2020

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RESEARCH ARTICLE Open Access

Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers

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Abstract

Background: The presence of comorbidity affects the care of cancer patients, many of whom are living with multiple comorbidities. The prevalence of cancer comorbidity, beyond summary metrics, is not well known. This study aims to estimate the prevalence of comorbid conditions among cancer patients in England, and describe the association between cancer comorbidity and socio-economic position, using population-based electronic health records.

Methods: We linked England cancer registry records of patients diagnosed with cancer of the colon, rectum, lung or Hodgkin lymphoma between 2009 and 2013, with hospital admissions records. A comorbidity was any one of fourteen specific conditions, diagnosed during hospital admission up to 6 years prior to cancer diagnosis. We calculated the crude and age-sex adjusted prevalence of each condition, the frequency of multiple comorbidity combinations, and used logistic regression and multinomial logistic regression to estimate the adjusted odds of having each condition and the probability of having each condition as a single or one of multiple comorbidities, respectively, by cancer type.

Results: Comorbidity was most prevalent in patients with lung cancer and least prevalent in Hodgkin lymphoma patients. Up to two-thirds of patients within each of the four cancer patient cohorts we studied had at least one comorbidity, and around half of the comorbid patients had multiple comorbidities. Our study highlighted common comorbid conditions among the cancer patient cohorts. In all four cohorts, the odds of having a comorbidity and the probability of multiple comorbidity were consistently highest in the most deprived cancer patients.

Conclusions: Cancer healthcare guidelines may need to consider prominent comorbid conditions, particularly to benefit the prognosis of the most deprived patients who carry the greater burden of comorbidity. Insight into patterns of cancer comorbidity may inform further research into the influence of specific comorbidities on socio-economic inequalities in receipt of cancer treatment and in short-term mortality.

Keywords: Cancer, Comorbidity, Multimorbidity, Deprivation, Prevalence, England, Epidemiology

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Background

Comorbidity refers to the existence of a long-term health condition in the presence of a primary disease of interest [1]. Having one or more comorbidities may influence the patient's prognosis for a primary disease such as cancer. Comorbidity may influence the timing of cancer diagnosis, in either a positive or a negative way. For example, the symptoms of comorbidity may drive a patient to seek medical care sooner, potentially leading to an earlier diagnosis. Alternatively, cancer symptoms may be mistakenly considered as symptoms of a pre-existing health condition, and could delay diagnosis [2–4]. Following diagnosis, the presence of comorbidity may also influence timing, receipt, or outcome of treatment, with clear evidence that those with comorbidity are less likely to receive curative treatment than those without, despite increasing evidence that many patients with comorbidity benefit from such treatment [3]. Although the presence of multiple co-existent health conditions is commonplace, the guidelines, funding and structures of primary care may not support the care of more patients with multiple conditions [5], and care in secondary and tertiary centres is typically highly siloed [3].

Methods used in the scientific literature to describe, measure and quantify the status of comorbidity as an explanatory factor in adverse disease outcomes are varied. Many summarised metrics of comorbidity have been proposed, providing an overall picture of a patient's comorbidity status, some specific to a primary disease while others are more general. For example, a widely used metric of comorbidity in epidemiological studies is the Charlson Comorbidity Index (CCI) [6], which weights 19 long-term health conditions according to their relative risk of one-year mortality, to produce an overall index score.

In this study, we firstly aimed to examine the prevalence of comorbid conditions in cancer patients using English population-based electronic health records of patients diagnosed with cancer of the colon, rectum, or lung or with Hodgkin lymphoma (HL). An association between comorbidity (not specific to any primary disease of interest) and socio-economic position has been widely reported: the prevalence of certain specific comorbid conditions [7–10] and general comorbidity prevalence being higher in deprived groups of patients [11–13]. Our second aim was to describe patterns of comorbidities and multiple comorbidity in these cancer patient cohorts, according to patient characteristics such as socio-economic position (deprivation).

Methods

We defined a comorbid condition as one of the following fourteen health conditions: myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), dementia, chronic obstructive pulmonary disease (COPD), rheumatological conditions, liver disease, diabetes, hemiplegia or paraplegia, renal disease, previous malignancy, obesity or hypertension. The conditions, selected following a systematic search of the data, included conditions of the Charlson Comorbidity Index [6] and any highly prevalent conditions that may influence cancer management alone or in combination with another condition.

Data

This study used England National Cancer Registry data of 331,655 patients aged 15–90 years at diagnosis with cancer of the colon, rectum, lung or Hodgkin's lymphoma, between 2009 and 2013. Registry data provided information on patient sex, age at diagnosis, site of cancer, date of cancer diagnosis and area of residence at time of diagnosis, which was used to derive socio-economic position, based on deprivation quintiles of the Income Domain of the Indices of Multiple Deprivation [14]. The five-level, ordinal variable indicates the level of deprivation from 1 (least deprived) to 5 (most deprived). Areas of residence are defined at the Lower Super Output Area level (mean population 1500).

Inpatient, outpatient and emergency hospital admissions records (Hospital Episode Statistics, HES) [15] were successfully linked with over 99% of the cancer registry records, using common unique variables present in both data sources. The International Statistical Classification of Diseases and Related Health Conditions tenth edition (ICD-10) [16] codes captured within the diagnostic fields of HES records provided information on health conditions recorded during hospital admissions. We used the ICD-10 code groupings of health conditions proposed by Quan and colleagues for defining comorbidities using administrative data (see Additional file 1) [17], and used an algorithm [18] to identify whether these conditions had been recorded in the six-year period prior to cancer diagnosis. In contrast to the approach of Maringe and colleagues [18], we included diagnoses of conditions recorded up to 6 months prior to cancer diagnosis. We anticipated that first-time diagnoses of the conditions could occur in this period, and wanted to obtain the most complete picture of patient comorbidity. We used cancer registry data to identify whether a patient had been diagnosed with an unrelated malignancy up to 6 years before their diagnosis with the cancer of interest.

Descriptive data analysis

We calculated the prevalence of a comorbid condition within each of the four patient cohorts defined by cancer site, firstly as a crude measure, calculating the percentage of patients who had a recorded diagnosis of the comorbidity in HES records, and secondly adjusting for

age and sex to account for the older age demographic of cancer patient populations. Weights for this adjustment were obtained from 2011 UK census published population estimates of persons living in England [19].

Statistical analysis

Logistic regression models were used to estimate the odds ratio (OR) of having each comorbidity by cancer site, adjusting for sex, age at cancer diagnosis and deprivation group. The binary outcome variable indicated the presence of the comorbidity. To account for a non-linear association between increasing age and the presence of comorbidity, age was modelled as a continuous variable using a restricted cubic spline with one knot fixed at 70 years in analyses conducted for cancers of the colon, rectum and lung and at 45 years for HL (the knot position was chosen as to be close to the mean age of the patients in each of these cancer cohorts). To reduce the risk of unstable models, we ensured there were at least ten or more occurrences of a comorbidity within the specific cancer patient cohort for every parameter of the model (events per variable, EPV) [20].

Multinomial logistic regression was used to estimate the probability of having a given comorbidity, either in isolation, or as one of multiple comorbidities, according to cancer site. The three-category outcome variable indicated whether the patient did not have the given comorbidity, only had this comorbidity, or had this comorbidity with other comorbidities. Models were adjusted for age, sex and deprivation, and were run for each cancer site and comorbidity combination with at least ten EPV.

All data analyses were conducted in STATA v.15.1 [21].

Results

Patient characteristics

The characteristics of patients diagnosed with cancer of the colon ($N = 102,216$), rectum ($N = 56,342$), lung ($N = 165,677$) or with HL ($N = 7420$) between 2009 and 2013, stratified by comorbidity status, are shown in Table 1. The majority of patients in each cohort were male: approximately 55% of colon, lung and HL patients and 63% of rectal cancer patients. At least 80% of colon, rectum and lung cancer patients were in the two oldest age group categories, while 50% of the HL patients were within the two youngest age groups. There was an even distribution of patients among each of the deprivation groups, except among lung cancer patients, where the percentage of patients in each group increased with deprivation level.

Comorbidity was over twice as prevalent in lung cancer patients than in patients with HL: 67% of lung cancer patients had one or more comorbidities versus almost 30% of HL patients. Similar patterns in comorbidity prevalence were seen in males and females. The prevalence of either single or multiple comorbidity rose with increasing age. Single comorbidity was more common than multiple comorbidity in the younger age groups, whereas in the older patients the opposite was observed. For example, approximately 29.2% of lung cancer patients aged 15–29 years had one comorbidity and 3.4% had multiple comorbidities, while in lung cancer patients aged 75–90 years the percentage of patients with one comorbidity or with multiple comorbidities were 26.9 and 49.9%, respectively.

The prevalence of multiple comorbidity increased with deprivation level in colon, rectum and lung cancer patients, but there was no pattern with deprivation in HL patients or in the prevalence of one comorbidity. For example, from 24.7 to 25.7% of rectal cancer patients had one comorbidity, while 17.7 to 27.6% of patients had multiple comorbidities.

Crude and adjusted prevalence of comorbidities at the time of cancer diagnosis

Across all cancer patient cohorts, hypertension, COPD, diabetes, CVD, CHF and PVD were among the most commonly recorded comorbid conditions. Adjusting for age and sex strongly impacted the prevalence of some comorbid conditions in colon, rectum and lung cancer patients (Fig. 1). The three most prevalent comorbidities in all four cancer patient cohorts were hypertension, COPD and diabetes. The adjusted prevalence of hypertension and of diabetes was similar among patients in each of the four cohorts (approximately 15–20% of patients had hypertension while approximately 5% of patients had diabetes). However, the adjusted prevalence of COPD was markedly higher in patients with lung cancer: approximately 25% of lung cancer patients had COPD versus 10% of patients in the other patient cohorts. Similarly, in comparison between the four cohorts, the prevalence of several other conditions (CVD, CHF, PVD or previous malignancy) was highest among the lung cancer patients.

Combinations of multiple comorbidity

The relative frequency (%) in which five of the most common conditions (COPD, diabetes, CVD, CHF and PVD) are present either as a single comorbidity or in combination with ten other common comorbid conditions is shown in Fig. 2. For a given cancer (identified by colour), the denominator is the number of patients with the comorbid condition, as represented on the y-axis, and the numerator is the number of those patients who had the condition as a single comorbidity or who had another condition, as depicted by the x-axis. Patients

Table 1 Patient characteristics according to comorbidity status, by cancer

	Cancer																											
	Colon								Rectum								Lung								Hodgkin lymphoma							
	All patients		Number of patient comorbidities						All patients		Number of patient comorbidities						All patients		Number of patient comorbidities						All patients		Number of patient comorbidities					
			0		1		2+				0		1		2+				0		1		2+				0		1		2+	
	N	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Sex																																
Male	54,425	53.2	23,455	43.1	14,887	27.4	16,083	29.6	35,630	63.2	18,782	52.7	8850	24.8	7998	22.4	91,568	55.3	29,333	32.0	25,283	27.6	36,952	40.4	4163	56.1	2907	69.8	697	16.7	559	13.4
Female	47,791	46.8	21,339	44.7	13,878	29.0	12,574	26.3	20,712	36.8	11,044	53.3	5299	25.6	4369	21.1	74,109	44.7	24,661	33.3	21,536	29.1	27,912	37.7	3257	43.9	2307	70.8	573	17.6	377	11.6
Age at cancer diagnosis (years)																																
15–29	769	0.8	661	86.0	103	13.4	5	0.7	207	0.4	180	87.0	22	10.6	5	2.4	178	0.1	120	67.4	52	29.2	6	3.4	2111	28.5	1885	89.3	205	9.7	21	1.0
30–44	2666	2.6	2151	80.7	416	15.6	99	3.7	1552	2.8	1302	83.9	203	13.1	47	3.0	1757	1.1	1212	69.0	435	24.8	110	6.3	1660	22.4	1412	85.1	194	11.7	54	3.3
45–59	11,971	11.7	8035	67.1	2619	21.9	1317	11.0	9597	17.0	7143	74.4	1635	17.0	819	8.5	19,923	12.0	10,768	54.0	5574	28.0	3581	18.0	1461	19.7	1001	68.5	288	19.7	172	11.8
60–74	42,166	41.3	20,696	49.1	11,696	27.7	9774	23.2	25,230	44.8	14,073	55.8	6421	25.4	4736	18.8	75,085	45.3	25,973	34.6	22,241	29.6	26,871	35.8	1398	18.8	651	46.6	366	26.2	381	27.3
75–90	44,644	43.7	13,251	29.7	13,931	31.2	17,462	39.1	19,756	35.1	7128	36.1	5868	29.7	6760	34.2	68,734	41.5	15,921	23.2	18,517	26.9	34,296	49.9	790	10.6	265	33.5	217	27.5	308	39.0
Deprivation group (IMD income)																																
Least deprived	22,411	21.9	10,864	48.5	6331	28.2	5216	23.3	11,879	21.1	6839	57.6	2939	24.7	2101	17.7	23,066	13.9	8589	37.2	6528	28.3	7949	34.5	1339	18.0	980	73.2	217	16.2	142	10.6
2	22,623	22.1	10,484	46.3	6303	27.9	5836	25.8	12,222	21.7	6810	55.7	3031	24.8	2381	19.5	28,411	17.1	9913	34.9	8025	28.2	10,473	36.9	1428	19.2	1013	70.9	222	15.5	193	13.5
3	21,591	21.1	9460	43.8	6123	28.4	6008	27.8	11,750	20.9	6219	52.9	2970	25.3	2561	21.8	32,822	19.8	10,980	33.5	9365	28.5	12,477	38.0	1462	19.7	1018	69.6	263	18.0	181	12.4
4	19,940	19.5	8118	40.7	5614	28.2	6208	31.1	11,266	20.0	5646	50.1	2838	25.2	2782	24.7	39,220	23.7	12,356	31.5	10,885	27.8	15,979	40.7	1618	21.8	1132	70.0	277	17.1	209	12.9
Most deprived	15,651	15.3	5868	37.5	4394	28.1	5389	34.4	9225	16.4	4312	46.7	2371	25.7	2542	27.6	42,158	25.4	12,156	28.8	12,016	28.5	17,986	42.7	1573	21.2	1071	68.1	291	18.5	211	13.4
TOTAL	102,216	100.0	44,794	43.8	28,765	28.1	28,657	28.0	56,342	100.0	29,826	52.9	14,149	25.1	12,367	21.9	165,677	100.0	53,994	32.6	46,819	28.3	64,864	39.2	7420	100.0	5214	70.3	1270	17.1	936	12.6

Abbreviations - *IMD* Indices of Multiple Deprivation

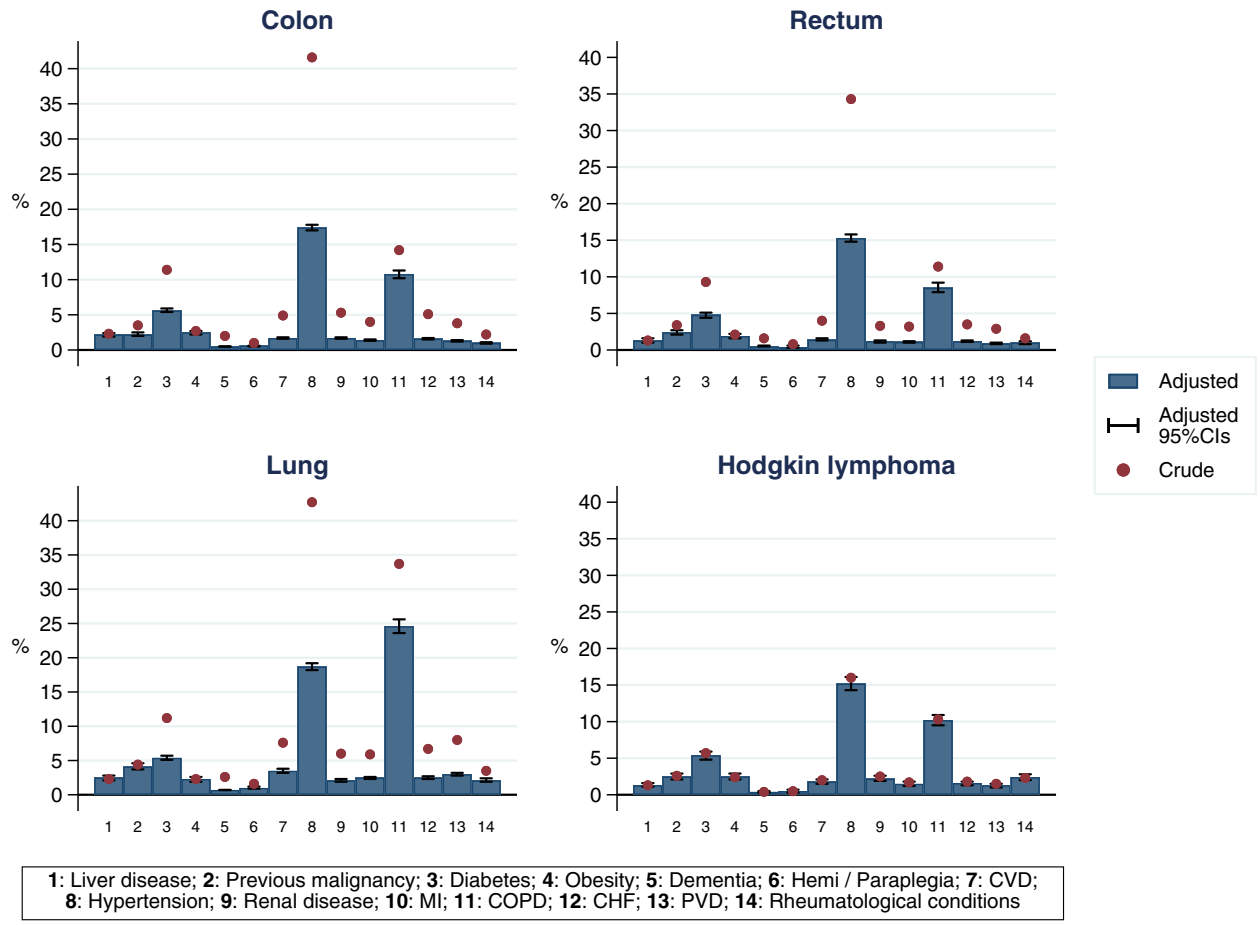

Fig. 1 Crude and adjusted prevalence (%) of fourteen comorbidities among cancer patients in England, by cancer

with two or more of the x-axis conditions are represented in the numerator for each condition.

Approximately one third of colorectal and lung cancer patients with COPD, and over half of HL patients with COPD, had this condition as a single comorbidity. By comparison, under one fifth of patients with diabetes, CVD, CHF and PVD had these conditions as a single comorbidity. CHF was the condition least frequently observed as a single comorbidity across all four cancer sites (89% or more of patients with CHF had additional comorbidities).

Hypertension was the condition most commonly present with each of comorbidities for which cross tabulations were investigated. In each of the cancer cohorts, approximately three-quarters of patients with CHF, and a similar proportion with CVD, also had hypertension. COPD was most commonly seen in combination with diabetes, CVD, CHF or PVD in lung cancer patients: while over 50% of lung cancer patients with CHF also had COPD, around one third of patients with HL, colon or rectal cancers with CHF also had COPD.

Multivariate analysis

The odds ratios derived from logistic regression of each comorbid condition being present at the time of cancer diagnosis, by cancer site, for females relative to males, age (relative to age 70 in colon, rectal and lung cancer patients, and relative to age 45 in HL patients) and increasing deprivation, adjusted for the other listed variables, are shown in Table 2. Analyses conducted for patients with HL were restricted to the comorbidities of diabetes, hypertension and COPD, as the prevalence counts of the other conditions did not adhere to the minimum of ten EPV required for the analyses.

Female patients with colon, rectal or lung cancer had up to 29% increased adjusted odds of having dementia (rectal cancer: OR 1.29; 95%CI 1.13, 1.48), up to 34% increased adjusted odds of having a previous malignancy (rectal cancer: OR 1.34; 1.23, 1.47) and approximately twice the adjusted odds of having rheumatological conditions (colon cancer: OR 2.16; 1.98, 2.36) compared to male patients. Conversely, compared with male patients in their respective cohort, females had significantly reduced adjusted odds of having diabetes, hemiplegia or

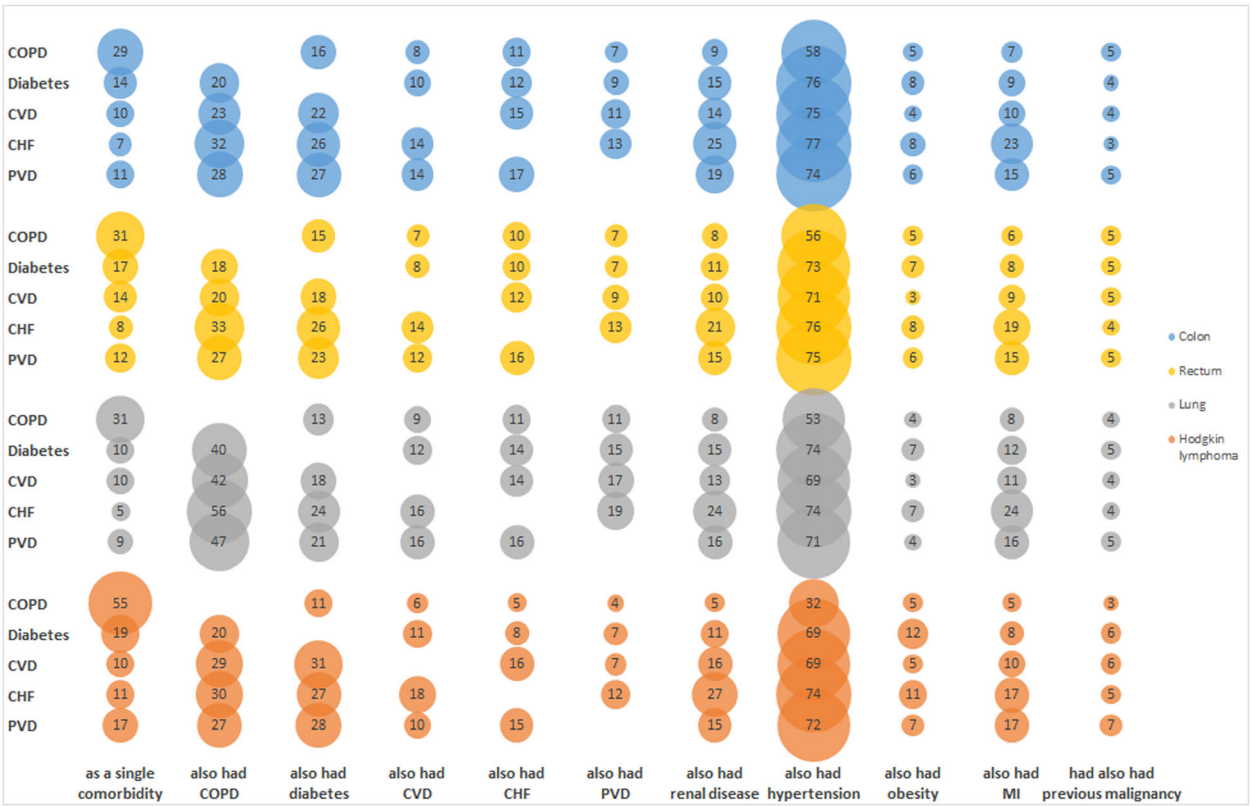

Fig. 2 Relative frequency (%) of five common conditions as a single comorbidity or with another comorbidity, by cancer

paraplegia, CVD, renal disease, MI, CHF or PVD. Across all four cancer cohorts, female patients had up to 38% reduced odds of having diabetes (HL: OR 0.62; 95%CI 0.50, 0.77).

The adjusted odds of dementia, CVD, hypertension, renal disease, MI and CHF being present at diagnosis consistently increased with age. For example, with 70-year old patients as the reference, colon cancer patients aged 45 had 87% reduced adjusted odds of CVD (OR 0.13; 0.13, 0.13) and 88% reduced adjusted odds of CHF (OR 0.12; 0.12, 0.12), while 90-year old patients had over three times the adjusted odds of CVD (OR 3.27; 2.69, 3.99) and over four times the adjusted odds of CHF (OR 4.72; 3.63, 6.13). There was no trend with age in colon, rectal or lung cancer patients for liver disease, having had a previous malignancy, diabetes or obesity. In lung cancer patients, no trend was observed with age for having COPD.

For at least eleven of the fourteen conditions, the adjusted odds of having the comorbid condition increased with the level of deprivation in colon, rectal or lung cancer patients. Obesity, dementia, hemiplegia, CVD, hypertension, renal disease, MI, COPD, CHF and PVD were associated with deprivation level in all three cancer cohorts. For example, the most deprived groups of lung cancer and colon cancer patients had approximately twice the adjusted odds of having COPD compared with the least deprived groups (OR 1.96; 1.89, 2.03 and OR 2.01; 1.89, 2.12 in the most deprived patients with lung or colon cancer, respectively). No trend with deprivation was seen with rheumatological conditions or with having a previous malignancy.

Probability of having single or multiple comorbidity at the time of cancer diagnosis

The graphs depicted in Fig. 3 show the adjusted probability of patients having one of the nine most common comorbid conditions recorded (hypertension, COPD, diabetes, CHF, CVD, PVD, MI, obesity or rheumatological conditions) at the time of colon cancer diagnosis, either as a single comorbidity, or as one of multiple comorbidities, according to age at cancer diagnosis and deprivation group (the least and most deprived groups), as derived from multinomial logistic regression.

With the exception of COPD, there was little difference between the most and least deprived groups in the probability of having each of the conditions as a single comorbidity. Among those patients with COPD as a single comorbidity, the difference in probability between

Table 2 Odds ratios of condition being present, by cancer (adjusted for other listed variables)

	Liver disease	Previous malignancy	Diabetes	Obesity	Dementia	Hemi- or paraplegia	CVD	Hyper-tension	Renal disease	MI	COPD	CHF	PVD	Rheum. conditions
	OR (95% CIs)													
	Colon cancer													
Sex														
Male [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.99 (0.91, 1.07)	1.23 (1.16, 1.32)	0.72 (0.69, 0.75)	0.94 (0.87, 1.01)	1.19 (1.09, 1.30)	0.70 (0.62, 0.79)	0.80 (0.75, 0.85)	0.90 (0.87, 0.92)	0.75 (0.71, 0.80)	0.48 (0.45, 0.51)	1.05 (1.01, 1.09)	0.66 (0.63, 0.70)	0.45 (0.42, 0.48)	2.16 (1.98, 2.36)
Age at cancer diagnosis (years)														
45	1.18 (1.13, 1.23)	0.40 (0.39, 0.41)	0.27 (0.25, 0.29)	0.79 (0.76, 0.82)	0.02 (0.02, 0.02)	0.39 (0.38, 0.39)	0.13 (0.13, 0.13)	0.14 (0.12, 0.16)	0.15 (0.15, 0.15)	0.12 (0.11, 0.12)	0.55 (0.49, 0.62)	0.12 (0.12, 0.12)	0.12 (0.12, 0.13)	0.22 (0.22, 0.22)
60	1.13 (1.08, 1.17)	0.74 (0.70, 0.78)	0.64 (0.55, 0.73)	1.00 (0.95, 1.05)	0.18 (0.17, 0.18)	0.65 (0.65, 0.66)	0.46 (0.45, 0.47)	0.51 (0.33, 0.80)	0.41 (0.40, 0.42)	0.52 (0.50, 0.54)	0.72 (0.62, 0.83)	0.45 (0.43, 0.46)	0.43 (0.41, 0.44)	0.54 (0.53, 0.55)
70 [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
80	1.01 (0.98, 1.05)	1.05 (0.97, 1.12)	1.31 (1.00, 1.71)	0.74 (0.72, 0.77)	4.68 (4.49, 4.89)	1.49 (1.46, 1.53)	2.04 (1.80, 2.32)	1.88 (0.68, 5.21)	2.64 (2.30, 3.03)	1.60 (1.42, 1.80)	1.38 (1.05, 1.80)	2.43 (2.10, 2.80)	1.88 (1.66, 2.13)	1.64 (1.58, 1.71)
90	0.91 (0.88, 0.94)	0.71 (0.68, 0.75)	0.82 (0.69, 0.98)	0.17 (0.17, 0.17)	13.95 (12.35, 15.75)	1.42 (1.39, 1.45)	3.27 (2.69, 3.99)	2.13 (0.72, 6.26)	4.35 (3.50, 5.40)	2.26 (1.92, 2.65)	1.04 (0.84, 1.29)	4.72 (3.63, 6.13)	1.70 (1.52, 1.91)	1.31 (1.27, 1.36)
Deprivation group														
Least deprived [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	1.10 (0.96, 1.25)	1.03 (0.93, 1.14)	1.12 (1.05, 1.19)	1.09 (0.95, 1.24)	1.19 (1.03, 1.37)	1.25 (1.02, 1.54)	1.11 (1.01, 1.21)	1.08 (1.03, 1.12)	1.20 (1.09, 1.31)	1.09 (0.99, 1.21)	1.12 (1.06, 1.18)	1.07 (0.98, 1.17)	1.11 (1.00, 1.24)	1.08 (0.96, 1.23)
3	1.13 (0.99, 1.29)	0.99 (0.89, 1.09)	1.25 (1.18, 1.33)	1.56 (1.38, 1.76)	1.29 (1.11, 1.48)	1.47 (1.20, 1.79)	1.20 (1.09, 1.31)	1.18 (1.13, 1.23)	1.34 (1.23, 1.47)	1.21 (1.10, 1.34)	1.24 (1.18, 1.32)	1.16 (1.06, 1.27)	1.26 (1.14, 1.40)	0.95 (0.84, 1.08)
4	1.38 (1.22, 1.58)	1.03 (0.93, 1.15)	1.48 (1.39, 1.58)	1.73 (1.53, 1.95)	1.42 (1.23, 1.63)	1.47 (1.20, 1.80)	1.35 (1.23, 1.47)	1.32 (1.27, 1.38)	1.55 (1.42, 1.69)	1.33 (1.21, 1.47)	1.56 (1.47, 1.65)	1.38 (1.26, 1.50)	1.38 (1.25, 1.53)	1.00 (0.88, 1.14)
Most deprived	1.50 (1.31, 1.71)	1.13 (1.02, 1.26)	1.75 (1.64, 1.87)	1.91 (1.68, 2.16)	1.70 (1.47, 1.97)	2.29 (1.88, 2.79)	1.60 (1.46, 1.76)	1.54 (1.47, 1.61)	1.83 (1.67, 2.01)	1.55 (1.40, 1.72)	2.01 (1.89, 2.12)	1.67 (1.52, 1.83)	1.59 (1.42, 1.76)	0.99 (0.86, 1.14)

Table 2 Odds ratios of condition being present, by cancer (adjusted for other listed variables) *(Continued)*

	Liver disease	Previous malignancy	Diabetes	Obesity	Dementia	Hemi- or paraplegia	CVD	Hyper-tension	Renal disease	MI	COPD	CHF	PVD	Rheum. conditions
	OR (95% CIs)													
	Rectal cancer													
Sex														
Male [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Female	1.05 (0.91, 1.22)	1.34 (1.23, 1.47)	0.80 (0.75, 0.85)	1.17 (1.04, 1.32)	1.29 (1.13, 1.48)	0.66 (0.54, 0.81)	0.75 (0.69, 0.82)	0.95 (0.91, 0.99)	0.73 (0.66, 0.80)	0.52 (0.46, 0.58)	1.03 (0.97, 1.09)	0.72 (0.65, 0.79)	0.39 (0.34, 0.44)	1.97 (1.73, 2.25)
Age at cancer diagnosis (years)														
45	0.93 (0.91, 0.95)	0.42 (0.41, 0.43)	0.27 (0.26, 0.29)	0.69 (0.68, 0.71)	0.06 (0.06, 0.06)	0.39 (0.39, 0.40)	0.12 (0.12, 0.12)	0.13 (0.12, 0.15)	0.12 (0.12, 0.13)	0.11 (0.11, 0.11)	0.47 (0.43, 0.51)	0.12 (0.12, 0.12)	0.07 (0.07, 0.07)	0.30 (0.29, 0.30)
60	1.00 (0.98, 1.02)	0.68 (0.65, 0.71)	0.60 (0.54, 0.66)	0.95 (0.92, 0.98)	0.21 (0.21, 0.21)	0.60 (0.60, 0.60)	0.46 (0.45, 0.47)	0.49 (0.34, 0.71)	0.37 (0.36, 0.37)	0.49 (0.48, 0.51)	0.66 (0.59, 0.74)	0.44 (0.43, 0.44)	0.40 (0.39, 0.41)	0.58 (0.57, 0.59)
70 [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
80	0.98 (0.96, 1.00)	1.22 (1.13, 1.32)	1.37 (1.11, 1.71)	0.73 (0.71, 0.74)	5.57 (5.32, 5.84)	1.83 (1.81, 1.86)	2.14 (1.92, 2.39)	1.74 (0.71, 4.22)	2.61 (2.35, 2.90)	1.63 (1.48, 1.80)	1.46 (1.17, 1.83)	2.46 (2.21, 2.74)	1.80 (1.62, 1.99)	1.65 (1.60, 1.70)
90	1.11 (1.09, 1.13)	0.96 (0.90, 1.02)	0.83 (0.72, 0.95)	0.17 (0.17, 0.17)	13.80 (12.36, 15.40)	1.82 (1.79, 1.85)	4.07 (3.35, 4.94)	2.51 (0.86, 7.29)	5.14 (4.22, 6.26)	2.06 (1.82, 2.32)	1.29 (1.06, 1.58)	4.96 (4.04, 6.10)	2.24 (1.97, 2.54)	1.91 (1.84, 1.99)
Deprivation group														
Least deprived [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	1.00 (0.77, 1.28)	1.08 (0.94, 1.24)	1.14 (1.04, 1.26)	1.28 (1.06, 1.56)	1.10 (0.89, 1.37)	1.70 (1.20, 2.40)	1.13 (0.98, 1.30)	1.04 (0.99, 1.10)	1.06 (0.91, 1.24)	1.06 (0.91, 1.24)	1.14 (1.04, 1.25)	1.11 (0.95, 1.29)	1.06 (0.90, 1.24)	1.09 (0.89, 1.34)
3	1.50 (1.19, 1.89)	0.91 (0.79, 1.05)	1.29 (1.18, 1.42)	1.27 (1.04, 1.54)	1.21 (0.98, 1.50)	2.13 (1.52, 2.98)	1.39 (1.21, 1.60)	1.14 (1.07, 1.20)	1.26 (1.08, 1.46)	1.17 (1.00, 1.36)	1.36 (1.25, 1.49)	1.23 (1.06, 1.42)	1.11 (0.94, 1.30)	1.13 (0.92, 1.39)
4	1.33 (1.05, 1.69)	1.01 (0.88, 1.17)	1.60 (1.46, 1.75)	1.63 (1.35, 1.97)	1.30 (1.05, 1.60)	2.23 (1.59, 3.12)	1.51 (1.32, 1.74)	1.26 (1.19, 1.34)	1.34 (1.15, 1.55)	1.33 (1.14, 1.54)	1.62 (1.49, 1.76)	1.25 (1.07, 1.44)	1.34 (1.14, 1.57)	1.12 (0.91, 1.38)
Most deprived	1.77 (1.39, 2.24)	1.14 (0.99, 1.33)	1.80 (1.63, 1.97)	1.80 (1.48, 2.18)	1.63 (1.31, 2.02)	2.66 (1.89, 3.74)	1.78 (1.54, 2.05)	1.48 (1.39, 1.57)	1.57 (1.34, 1.83)	1.52 (1.30, 1.77)	2.25 (2.07, 2.46)	1.65 (1.42, 1.91)	1.59 (1.36, 1.87)	1.24 (1.00, 1.54)

Table 2 Odds ratios of condition being present, by cancer (adjusted for other listed variables) *(Continued)*

	Liver disease	Previous malignancy	Diabetes	Obesity	Dementia	Hemi- or paraplegia	CVD	Hyper-tension	Renal disease	MI	COPD	CHF	PVD	Rheum. conditions
	OR (95% CIs)													
	Lung cancer													
Sex														
Male [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.87 (0.82, 0.93)	1.11 (1.06, 1.16)	0.75 (0.73, 0.78)	1.12 (1.05, 1.20)	1.22 (1.15, 1.30)	0.81 (0.75, 0.88)	0.83 (0.80, 0.87)	0.98 (0.96, 1.00)	0.72 (0.69, 0.75)	0.60 (0.58, 0.63)	1.09 (1.07, 1.11)	0.76 (0.73, 0.80)	0.50 (0.48, 0.52)	1.98 (1.87, 2.09)
Age at cancer diagnosis (years)														
45	1.42 (1.35, 1.49)	0.83 (0.76, 0.89)	0.24 (0.23, 0.26)	0.70 (0.68, 0.71)	0.04 (0.04, 0.04)	0.43 (0.43, 0.43)	0.22 (0.21, 0.23)	0.12 (0.11, 0.14)	0.13 (0.13, 0.13)	0.19 (0.19, 0.20)	0.39 (0.31, 0.50)	0.16 (0.16, 0.17)	0.10 (0.09, 0.10)	0.29 (0.28, 0.29)
60	1.35 (1.29, 1.42)	0.93 (0.85, 1.01)	0.60 (0.52, 0.69)	0.97 (0.93, 1.00)	0.28 (0.28, 0.28)	0.75 (0.74, 0.76)	0.55 (0.52, 0.59)	0.49 (0.30, 0.80)	0.38 (0.36, 0.39)	0.62 (0.58, 0.66)	0.69 (0.47, 1.03)	0.47 (0.45, 0.50)	0.47 (0.43, 0.51)	0.70 (0.68, 0.73)
70 [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
80	0.80 (0.78, 0.82)	1.02 (0.92, 1.12)	1.24 (0.95, 1.63)	0.67 (0.65, 0.69)	4.37 (4.13, 4.63)	1.10 (1.07, 1.12)	1.56 (1.31, 1.85)	1.59 (0.57, 4.41)	2.48 (2.07, 2.97)	1.38 (1.19, 1.61)	1.10 (0.63, 1.94)	1.93 (1.62, 2.29)	1.47 (1.15, 1.87)	1.07 (1.02, 1.13)
90	0.54 (0.53, 0.55)	0.76 (0.71, 0.82)	0.82 (0.68, 0.99)	0.18 (0.18, 0.18)	13.22 (11.20, 15.60)	1.23 (1.20, 1.27)	2.26 (1.77, 2.88)	1.70 (0.59, 4.85)	4.16 (3.13, 5.53)	1.51 (1.28, 1.78)	0.80 (0.51, 1.24)	3.55 (2.63, 4.79)	1.08 (0.90, 1.30)	0.92 (0.88, 0.96)
Deprivation group														
Least deprived [REF]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	1.28 (1.13, 1.46)	0.95 (0.87, 1.03)	1.10 (1.04, 1.16)	1.19 (1.05, 1.36)	1.13 (1.01, 1.27)	1.38 (1.17, 1.62)	1.09 (1.01, 1.17)	1.02 (0.98, 1.05)	1.07 (1.00, 1.16)	1.08 (1.00, 1.17)	1.17 (1.12, 1.22)	1.11 (1.03, 1.19)	1.12 (1.05, 1.20)	1.09 (0.99, 1.20)
3	1.29 (1.14, 1.47)	0.89 (0.82, 0.96)	1.09 (1.03, 1.15)	1.27 (1.12, 1.45)	1.21 (1.09, 1.36)	1.50 (1.28, 1.76)	1.20 (1.12, 1.28)	1.04 (1.01, 1.08)	1.15 (1.07, 1.24)	1.16 (1.08, 1.25)	1.36 (1.31, 1.41)	1.15 (1.07, 1.23)	1.14 (1.07, 1.21)	1.04 (0.95, 1.14)
4	1.44 (1.27, 1.62)	0.84 (0.78, 0.91)	1.25 (1.18, 1.32)	1.51 (1.34, 1.70)	1.38 (1.24, 1.53)	1.76 (1.51, 2.04)	1.36 (1.27, 1.45)	1.13 (1.09, 1.17)	1.21 (1.13, 1.30)	1.28 (1.19, 1.38)	1.59 (1.53, 1.65)	1.30 (1.22, 1.39)	1.17 (1.10, 1.25)	1.08 (0.99, 1.18)
Most deprived	1.66 (1.48, 1.87)	0.88 (0.81, 0.95)	1.29 (1.23, 1.36)	1.69 (1.50, 1.90)	1.52 (1.37, 1.69)	2.17 (1.88, 2.52)	1.45 (1.36, 1.54)	1.22 (1.18, 1.27)	1.33 (1.24, 1.43)	1.33 (1.24, 1.43)	1.96 (1.89, 2.03)	1.35 (1.26, 1.44)	1.32 (1.24, 1.41)	1.05 (0.96, 1.14)

Table 2 Odds ratios of condition being present, by cancer (adjusted for other listed variables) *(Continued)*

	Liver disease	Previous malignancy	Diabetes	Obesity	Dementia	Hemi- or paraplegia	CVD	Hyper-tension	Renal disease	MI	COPD	CHF	PVD	Rheum. conditions
	OR (95% CIs)													
	Hodgkin lymphoma													
Sex														
Male [REF]	–	–	1.00	–	–	–	–	1.00	–	–	1.00	–	–	–
Female	–	–	0.62 (0.50, 0.77)	–	–	–	–	0.88 (0.76, 1.02)	–	–	1.05 (0.90, 1.23)	–	–	–
Age at cancer diagnosis (years)														
45 [REF]	–	–	1.00	–	–	–	–	1.00	–	–	1.00	–	–	–
60	–	–	3.36 (2.89, 3.91)	–	–	–	–	4.46 (3.00, 6.63)	–	–	1.68 (1.41, 2.00)	–	–	–
70	–	–	5.03 (4.04, 6.27)	–	–	–	–	8.78 (4.57, 16.86)	–	–	2.48 (1.94, 3.18)	–	–	–
80	–	–	5.74 (4.49, 7.33)	–	–	–	–	13.86 (5.84, 32.91)	–	–	2.62 (2.02, 3.39)	–	–	–
90	–	–	5.17 (4.13, 6.47)	–	–	–	–	18.13 (6.70, 49.03)	–	–	1.43 (1.23, 1.66)	–	–	–
Deprivation group														
Least deprived [REF]	–	–	1.00	–	–	–	–	1.00	–	–	1.00	–	–	–
2	–	–	1.19 (0.83, 1.72)	–	–	–	–	1.26 (1.00, 1.60)	–	–	1.17 (0.90, 1.52)	–	–	–
3	–	–	1.48 (1.03, 2.11)	–	–	–	–	1.43 (1.14, 1.81)	–	–	1.18 (0.91, 1.54)	–	–	–
4	–	–	1.89 (1.34, 2.67)	–	–	–	–	1.48 (1.18, 1.87)	–	–	1.37 (1.07, 1.77)	–	–	–
Most deprived	–	–	2.39 (1.69, 3.37)	–	–	–	–	1.96 (1.55, 2.48)	–	–	1.86 (1.45, 2.38)	–	–	–

Abbreviations - *CI* confidence intervals, *CVD* Cerebrovascular disease, *MI* Myocardial infarction, *COPD* Chronic obstructive pulmonary disease, *CHF* Congestive heart failure, *PVD* Pheripheral vascular disease, *REF* reference, *Rheum.* Rheumatological

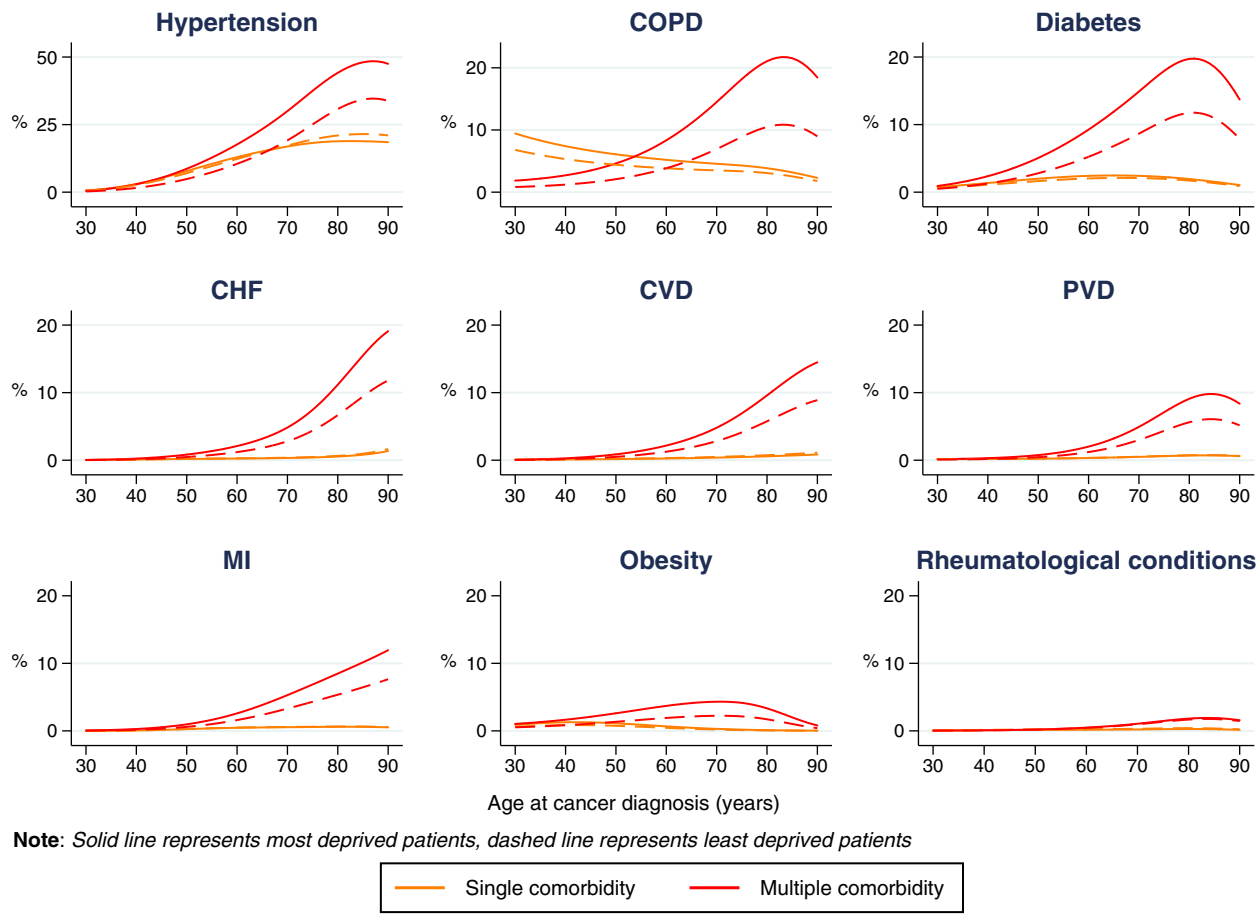

Fig. 3 Probability (%) of condition present as single or multiple comorbidity, by deprivation group (colon cancer)

the most and least deprived groups decreased with age. The most deprived patients had a higher probability of having each of the conditions as one of multiple comorbidities compared with the least deprived group, with one exception (rheumatological conditions). Generally, the difference in probability between the two deprivation groups was greatest in older age: it peaked at approximately 80 years for hypertension, COPD, diabetes, PVD and obesity, while in patients with CHF, CVD, and MI the difference continued to increase with age. Having rheumatological conditions was not associated with increasing age or deprivation level.

Similar patterns in the probability of having a comorbid condition according to deprivation group were observed for patients with rectal or lung cancers (Additional files 2 and 3).

Discussion

Our study is, to our knowledge, the first large-scale, population-based study describing comorbidity prevalence in cancer patient populations. Up to two-thirds of patients had at least one long-term health condition at the time of their cancer diagnosis, and around half of these comorbid cancer patients had multiple long-term conditions. There was evidence that many of the comorbid conditions we investigated were associated with socio-economic deprivation, and the most deprived groups of patients had a higher probability of having multiple comorbidities compared with the less deprived groups.

The choice of cancer sites we studied was based on aetiology of the cancer: three of the cancer sites (colon, rectum and lung) were associated with environmental risk factors including tobacco smoking [22, 23], alcohol use and diet [24, 25]. Furthermore, tobacco smoking is associated with certain conditions, such as COPD [26–28] and Type 2 diabetes [29, 30], and is also associated with socioeconomic position [31]. HL is linked to infection rather than environmental factors [22].

Hypertension, COPD and diabetes were the three most prevalent comorbidities in all four cancer patient cohorts, with a higher prevalence in the most deprived patients. The odds of having COPD from being in the

most deprived group of lung cancer patients (compared with being in the least deprived group – the 'deprivation gap') was 10% more than the deprivation gap in the adjusted odds of having COPD in the Hodgkin lymphoma patients. This may be reflective of the role of smoking in the aetiology of both lung cancer and COPD, and the higher prevalence of smoking in the more deprived population. The association between smoking status and deprivation is not quantifiable in the cancer patient cohorts as we did not have information on smoking prevalence.

Similar work using administrative data to describe comorbidity in cancer populations has been undertaken in New Zealand [32] and in Spain [33]. In the study of patients diagnosed with colon, rectal, breast, ovarian, uterine, stomach, liver, renal or bladder cancers in New Zealand ($N = 14,096$), commonly diagnosed comorbidities among colon and rectal cancer patients were hypertension, cardiac conditions and diabetes. In the Spanish cohort of colorectal cancer patients from the cancer registries of Girona and Granada ($N = 1061$), diabetes, COPD and CHF were the most common comorbidities. Comparing our study with the study in New Zealand, there were similarities among colon cancer patients in the age-sex adjusted prevalence of hypertension, while diabetes prevalence was higher in New Zealand. The adjusted prevalence of hypertension was 16.6%, uncomplicated diabetes was 5.9% and diabetes with complications was 5.0% among patients in New Zealand, while in our study the adjusted prevalence of hypertension was 17.4% and diabetes (with and without complications) was 5.7%. This supports our earlier assumption that less severe diabetes may be underreported in hospital admissions records. Given the 'gatekeeper' structure and functioning of the healthcare system in the UK [34] and the focus on managing diabetes within primary care [35], cases of diabetes recorded in hospital admissions are possibly those that are not controlled within available primary care resources [36] or present with complications. The Spanish study reported the crude prevalence of conditions among colorectal cancer patients, which were generally higher than the crude prevalence of conditions observed in our study. Diabetes was prevalent in 23.6% of colorectal cancer patients in this study, while in our study the crude prevalence of diabetes was 11.4% or 9.4% among colon or rectal cancer patients, respectively. Nonetheless, there was consistency between our study and both of these other studies in terms of common comorbid conditions among the patient cohorts.

In our study, approximately 13% of the HL cohort, over 21% of the colorectal cancer cohorts and over 39% of the lung cancer cohort had multiple comorbidities, while from 17 to 28% of patients in each cohort had a single comorbidity at the time of their cancer diagnosis. These findings are important given the impact comorbidity may have on cancer care, particularly where care is provided within the constraints of healthcare guidelines that are not designed for the simultaneous management of two or more chronic conditions or morbidities (i.e. "multimorbidity"). Scientific studies indicate that multimorbidity is regularly observed in the population [37–39] and poses a challenge to health care systems, particularly those geared towards single disease management [5, 40, 41]. Clinical guidelines in the United Kingdom are not accommodating to the cumulative impact of treatment recommendations on those with multiple morbidities, and do not facilitate a comparison of potential benefits or risks [42]. Patients with multiple chronic conditions have higher rates of healthcare consultations than those without [38, 43, 44]. Managing and treating comorbid conditions places an additional economic burden on healthcare systems. In one study of the costs per capita of several comorbid conditions, renal disease was identified as one of the most costly conditions to manage among cancer patients (approximately 174% of the costs of the cancer), while the cost of diabetes or heart disease was substantially lower (approximately 20% or 6% of cancer costs, respectively) [45]. The increase in costs also depends on the number and combination of comorbid conditions: among the cancer patients with diabetes in our study, between 10 and 15% of these patients also had renal disease.

In cancer patients, the presence of comorbidity can be influential on cancer management and therapeutic options. Patients with comorbidity may be less likely than those without comorbidity to receive curative treatment [3]. Treatment decisions made by clinicians may be weighted by the type and severity of comorbidity, for example, CHF has been reported to influence receipt of surgery for non-small cell lung cancer [46], receipt of adjuvant chemotherapy for colon cancer [47] and receipt of any treatment for prostate cancer [48]. The presence of COPD influenced receipt of surgical treatment in non-small cell lung cancer patients [46] and adjuvant therapy in colon cancer patients [47]. However, there is also evidence that comorbid patients who receive treatment have better prognosis for survival than those who do not receive treatment, as shown with the receipt of adjuvant therapy for colon cancer [47, 49]. Moreover, older cancer patients and patients with comorbidity have historically been under-represented in cancer clinical trials. This limits the applicability of cancer clinical trial results to a younger and healthier cohort of patients than clinicians are actually treating, meaning that while there is evidence suggesting that patients with comorbidity as a group are not receiving optimal cancer treatment, specific information required for clinical decision-making is often lacking [50]. We found a non-negligible increase in the prevalence of comorbidities when we

included diagnoses in the six-months prior to cancer diagnoses. While some of these conditions may have arisen in these months because of the cancer, their presence will be as relevant when considering treatment, irrespective of the timing of their diagnosis.

Our study showed socio-economic position to be an important factor associated with having one or more comorbid conditions at the time of cancer diagnosis, with comorbidity prevalence increasing with deprivation. It is possible that mechanisms within clinical guidelines and decision-making that lead to non-treatment of cancer patients with comorbidity disproportionately impact the more deprived patients. An existence of socio-economic inequalities in receipt of treatment has been identified [51, 52]. Reviewing the treatment process of cancer patients with comorbidity may therefore have a beneficial effect in reducing the socioeconomic inequalities in receipt of cancer treatment. Moreover, because cancer data contains mainly cancer-related outcomes, how the cancer and related treatments impact patient comorbidity and prognosis is not well known [3]. Having the resources and guidelines within which to manage patient comorbid conditions robustly during cancer treatment is one strategy for mitigating the risk of adverse patient outcomes occurring from comorbid disease. In England, socio-economic inequalities in cancer survival have narrowed little, despite the implementation of government strategies that intended to reduce these inequalities [53]. Focusing on the management of comorbidity in cancer patients could be one potential pathway to addressing socio-economic inequalities in cancer outcomes.

There are a variety of metrics of comorbidity in the scientific literature that are used to study the relationship between comorbidity on cancer outcomes, although no consensus has been reached on a gold standard measure of comorbidity within the context of cancer [54]. Many of the approaches provide a summary measure of the patient's comorbid conditions and the severity of these conditions. However, the prognostic impact of comorbidity can depend on the type and stage of the cancer [55]. In addition, the presence of comorbidity - particularly certain comorbid conditions - adds complexity to the provision of treatment for cancer. When investigating the relationship between comorbidity and cancer outcomes, a more granular approach investigating specific comorbid conditions in turn, rather than using a summary measure of comorbidity, could be more appropriate and insightful.

We acknowledge potential limitations in this study. We capture comorbidity information based on diagnoses of health conditions recorded during hospital admission(s) prior to cancer diagnosis, and are therefore reliant on patients requiring hospital-based medical attention for their health condition(s) in order to obtain this information. The potential for measurement error from the information recorded in the diagnostic fields of hospital admissions records should also be acknowledged. However, we assume that the more severe conditions are likely to be captured within the diagnostic fields. Underreporting may occur in less severe conditions, such as obesity, that are unlikely to be the primary reason for the hospital admission, and may occur more frequently with elderly patients or patients with more severe comorbidities, due to competing demands. Conditions such as less severe type II diabetes are possibly underreported. Further work comparing the prevalence of the conditions we studied in the cancer cohorts with the prevalence of these conditions in the general population in England, as reported in government publications and scientific literature, would be useful step in validating our results.

Our study of over 300,000 patients is one of the largest population-based studies of comorbidity prevalence among cancer patients, and one of the first such studies of patients in England. Using data from well-established sources, we were able to describe the prevalence of fourteen chronic health conditions among these cancer patients, and highlight an association between socio-economic position and prevalence of most of these conditions.

Conclusion

This study underlines that many comorbid cancer patients are living with multiple comorbidities, and that the most deprived patients carry the greater burden of comorbidity. Healthcare guidelines may not always encompass the simultaneous management of multiple chronic conditions, but guidelines for the management of cancer may need to consider some prominent comorbid conditions. Insight into patterns of cancer comorbidity informs further research into the influence of comorbidity - particularly the influence of specific comorbid conditions - on outcomes following cancer diagnosis, including socio-economic inequalities in receipt of treatment and short-term mortality.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12885-019-6472-9.

Additional file 1. Definition of the fourteen conditions, according to ICD-10 code classification. Table of the fourteen conditions and the ICD-10 code groupings used to define them.

Additional file 2. Probability (%) of condition present as single or multiple comorbidity, by deprivation group (lung cancer). Additional results in complement to those presented in Fig. 3: graphs representing the probability of having any of nine comorbid conditions in lung cancer patients.

Additional file 3. Probability (%) of condition present as single or multiple comorbidity, by deprivation group (rectal cancer). Additional results in complement to those presented in Fig. 3: graphs representing the probability of having any of nine comorbid conditions in rectal cancer patients.

Abbreviations

CCI: Charlson Comorbidity Index; CHF: Congestive Heart Failure; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CVD: Cerebrovascular Disease; EPV: Events Per Variable; HES: Hospital Episode Statistics; HL: Hodgkin lymphoma; ICD: International Classification of Diseases and Related Health Problems; MI: Myocardial infarction; OR: Odds Ratio; PVD: Peripheral Vascular Disease

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Authors' contributions

CM, MALF and HF contributed to the conception of the study. BR, HF, AB and LE designed the study. AB and ENN provided advice on statistical methods. HF conducted the analyses of the data and prepared the draft of the manuscript, tables and figures. BR, AB, and LE supervised the study and provided comments on the manuscript draft. CM, MALF, NN and DS provided comments on the final draft of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available via application to the Public Health England Office for Data Release, but restrictions apply to the availability of these data.

Ethics approval and consent to participate

We obtained the statutory approvals required for this research from the Confidentiality Advisory Group (CAG) of the Health Research Authority (HRA): PIAG 1–05(c) 2007.
Ethical approval was obtained from the Research Ethics Committee (REC) of the Health Research Authority (HRA): 07/MRE01/52.
This work uses data provided by patients and collected by the National Health Service as part of their care and support. We used anonymised National Cancer Registry and Hospital Episode Statistics data. No consent to participate was sought from patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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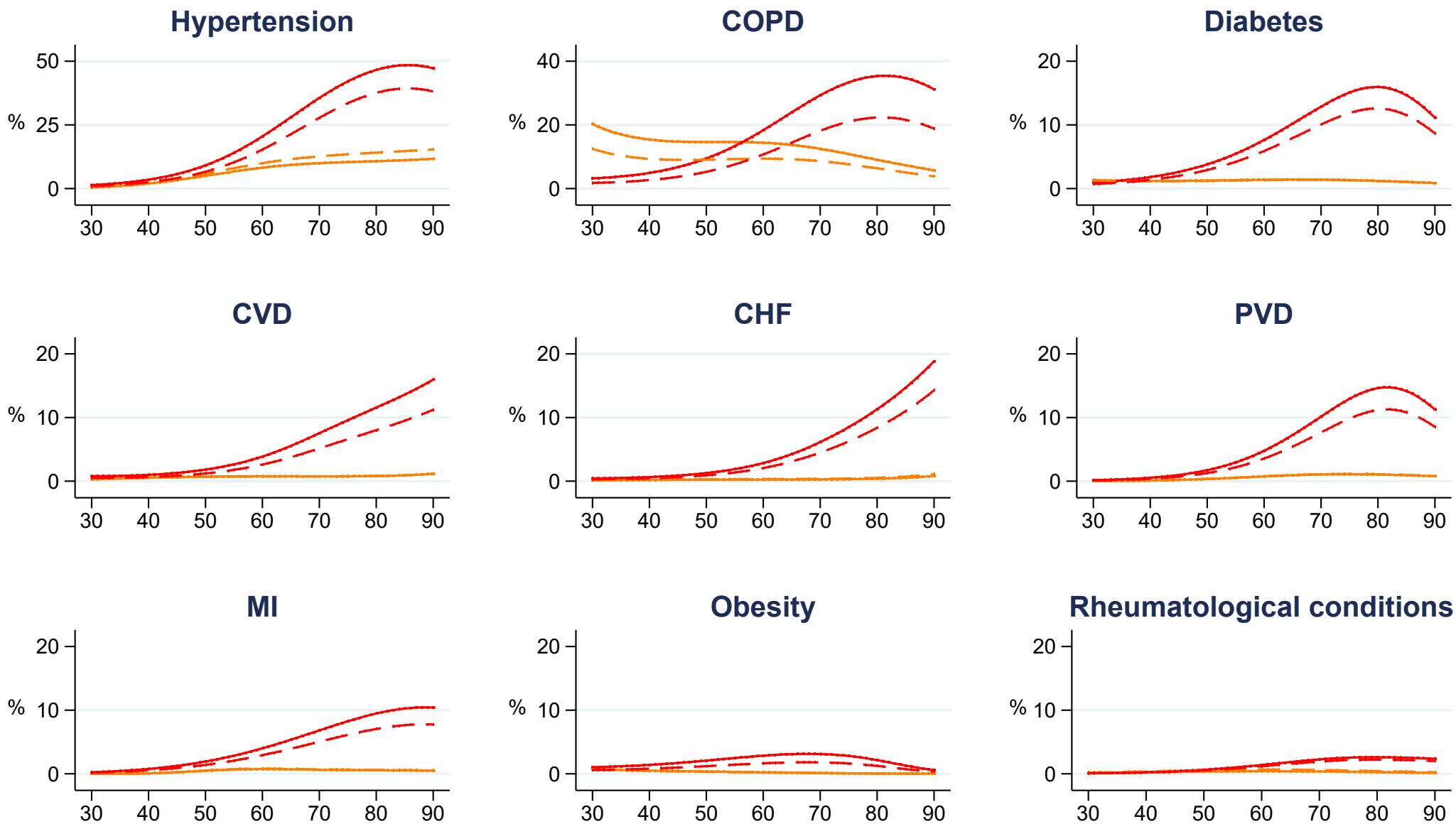
Publisher's Note

Additional file 1: Definition of the fourteen conditions, according to ICD-10 code classification

Condition	ICD-10 codes
Liver disease	B18, I850, I859, I864, I982, K700, K701, K702, K703, K704, K709, K711, K713, K714, K715, K717, K721, K729, K73, K74, K760, K762, K763, K764, K765, K766, K767, K768, K769, Z944
Previous malignancy	CXX, excluding related same site malignancy
Diabetes	E100, E101, E102, E103, E104, E105, E106, E107, E108, E109, E110, E111, E112, E113, E114, E115, E116, E117, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147
Obesity	E66
Dementia	F00, F01, F02, F03, F051, G311, G30
Hemiplegia or paraplegia	G041, G114, G801, G802, G81, G82, G830, G831, G832, G833, G834, G839
Cerebrovascular disease	G45, G46, H340, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69
Hypertension	I10, I119, I129, I139
Renal disease	I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N18, N19, N250, Z490, Z491, Z492, Z940, Z992
Myocardial infarction	I21, I22, I252
Chronic obstructive pulmonary disease	I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703
Congestive heart failure	I43, I50, I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, P290
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Rheumatological conditions	M05, M06, M315, M32, M33, M34, M351, M353, M360

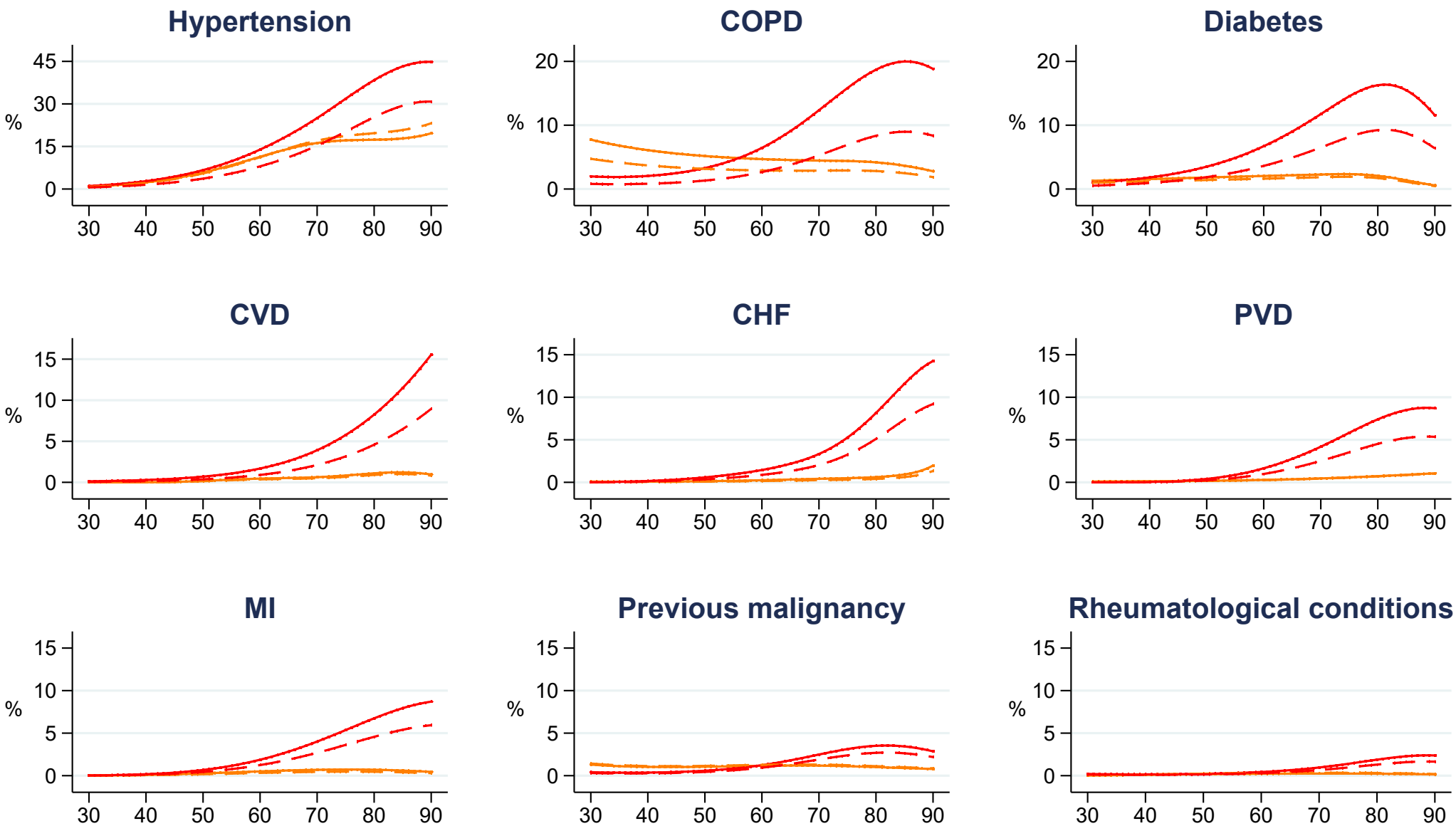
Abbreviations - ICD: International Classification of Diseases and Related Health Problems;
Source: Quan et al (2005)

Additional file 2: Probability (%) of condition present as a single or multiple comorbidity, by deprivation group (**Lung cancer**)



Note: *Solid line represents most deprived patients, dashed line represents least deprived patients*

Additional file 3: Probability (%) of condition present as a single or multiple comorbidity, by deprivation group (**Rectal cancer**)



Note: *Solid line represents most deprived patients, dashed line represents least deprived patients*

Evaluating the measurement of comorbidity prevalence

Background

As previously discussed in this thesis, the impact of comorbidity across the cancer patient pathway is wide-reaching. Patients with comorbidity are, generally, more likely to have been diagnosed with cancer via emergency presentation,[128] and less likely to receive curative cancer treatment than patients without comorbidity.[13] Comorbidity is a prognostic factor in cancer survival,[92, 109] the extent to which depends on the type of comorbidity and cancer[116] and stage of disease.[110] Additionally, comorbidity is more prevalent among the older population, in which the majority of cancers occur.[129] The prevalence of comorbidity tends to be higher among the most socio-economically deprived;[14, 130] which was also observed in the population-based study of cancer patients described in Research Paper 2.[127] These elements have important implications on cancer care in these populations.

The availability of reliable data on comorbidity in cancer patients facilitates the effective investigation of the role of comorbidity in cancer patient outcomes.[104] Sources of information on cancer comorbidity vary, from administrative data sources to information collected during prospective cohort studies of cancer patients or cancer treatment clinical trials, or information contained within health survey data. In the scientific literature, information on cancer comorbidity is commonly sourced from routine, administrative data, such as primary or secondary care data. By their nature, these data potentially cover the largest cancer patient populations, and therefore offer greater generalisability to all cancer patients, as compared with other sources of information on cancer comorbidity.[131] However, there has been concern regarding possible under-recording of some conditions in administrative data sources.[131, 132]

In Research Paper 2, information from hospital admissions records (Hospital Episode Statistics, HES[71]) was used to estimate the crude and adjusted prevalence of thirteen chronic conditions among England cancer registry cohorts of patients, retrospective to their cancer diagnosis. The study described here draws upon this work undertaken for Research Paper 2, with the aim of evaluating hospital admissions data as a source of information on cancer comorbidity prevalence, based upon the prevalence of the conditions among England cancer registry cohorts of colorectal cancer, lung cancer and Hodgkin lymphoma patients prior to their cancer diagnosis.

The first objective of this study was to undertake a review of the scientific literature to find studies that reported information on the prevalence of these thirteen conditions among population-based cohorts of colorectal cancer patients. This was done in order to compare and contrast sources of comorbidity prevalence information from these studies with the prevalence of the comorbidities among the England cancer registry cohort of colorectal cancer patients. The second objective was to undertake a review of the grey literature (including government web-based resources) and scientific literature to obtain information on the national prevalence of these conditions among the general population in England, as a reference point with which to compare the prevalence of these conditions among the three England cancer registry cohorts of patients. The hypothesis for this second objective was that the prevalence of many of the conditions could reasonably be higher among pre-cancer cohorts of patients than among the general population, given that certain types of cancer share similar aetiological risk factors with some of the conditions studied.

Methods

The health conditions of interest included non-cancer conditions of the Charlson Comorbidity Index (CCI),[83] or any non-CCI conditions that were highly prevalent in our data and that may impact

treatment for cancer. The thirteen conditions that were investigated were: myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), dementia, chronic obstructive pulmonary disease (COPD), rheumatological conditions, liver disease, diabetes, hemiplegia or paraplegia, renal disease, obesity and hypertension.

Cancer patient data

The patient data that were used to estimate the prevalence of these thirteen conditions were the same data used in the study described in Research Paper 2.[127] Data were analysed as three separate patient cohorts (according to cancer type), using national cancer registry records of 331,655 patients aged 15-90 years diagnosed with either colorectal cancer (N=158,588), lung cancer (N=165,677) or Hodgkin lymphoma (HL) (N=7,420) between 2009 and 2013, linked with HES data of Inpatient, Outpatient and Accident & Emergency hospital admissions.

Data analysis

The crude and adjusted prevalence of each condition was estimated using the same methods described in Research Paper 2.[127] Crude prevalence was based on the percentage of patients that had been diagnosed with the condition. The age-sex adjusted prevalence, and corresponding 95% confidence intervals, were estimated using weights for each year of age and sex based on published population estimates from the 2011 UK census.[133] Adjustment for age and sex facilitated the comparison of the prevalence of comorbid conditions in the cancer patient cohorts with the observed or estimated prevalence of these conditions in the general population (derived from the literature search).

Literature search

The literature search strategy for the first objective was to search the EMBASE, MEDLINE and PUBMED databases for studies published in the scientific literature reporting the prevalence of the conditions of interest among colorectal cancer patients (Table 4.1). For the second objective, the strategy was to search government websites, the grey literature and the published scientific literature for information on the national prevalence of the conditions in England. For the latter, where information was available from multiple sources, priority was given to that representing official national prevalence statistics (such as information available from government sources). The intention of the study was to report the prevalence information obtained from the literature, and to compare it with the prevalence among the England cancer registry cohorts (i.e. based on information derived from the HES data).

Table 4-1: Search criteria to obtain information on prevalence

Objective	**Databases / sources**	**Search criteria**
1. Prevalence of conditions among colorectal cancer patients	- EMBASE - MEDLINE - PUBMED	- Adult cancer patients; - Colorectal cancer diagnosis from 2000 onwards - Population-based studies

2. Prevalence of conditions among the general population in England	- Government web-based sources, including:
	  - Public Health England,
	  - Office for National Statistics
	- Open Grey
	- EMBASE
	- MEDLINE
	- PUBMED
		- Adults
		- Reported from 2000 onwards
		- Relates to England (or UK)
		- Nationally-representative sample

Data sources of prevalence information

Objective 1 – Prevalence among colorectal cancer patients

From the literature search it was possible to find prevalence information on all thirteen conditions (Appendix Table 1). Six studies reported information on nine or more of the thirteen conditions of interest. These studies were undertaken in England,[48] Spain,[117, 134] New Zealand[116] or the United

States.[135, 136] With the exception of the cross-sectional study by Luque-Fernandez and colleagues,[117] these studies were retrospective cohort studies. Other studies undertaken in the United States,[137-139] Iran, [140] Denmark,[52] Canada[141] and Australia[142] reported information on one or two of the conditions. The majority of these studies were population-based, with study populations derived from cancer registration data, while three studies were based upon the data of patients attending clinics or treatment centres,[137, 139, 140] and the Australian study was based on people (both with and without a cancer diagnosis) recruited to a prospective cohort study of diet and lifestyle in Melbourne. The reported age range of patients varied between studies: some studies focused on older age groups only, or others studied different age ranges of adult populations (e.g. one study had a lower age range of 15 years while in another the youngest patients were 25 years old).

Information on comorbidity was commonly obtained from administrative data sources, such as hospital records or primary care data. Several United States-based studies derived this information from Medicare claims data. Medicare is the United States federal government's health insurance programme for people who are 65 years or older or for people with certain disabilities or End-Stage Renal Disease.[143] Prospective cohort studies captured information on the comorbidity via diagnostic testing or examination at the time of recruitment. In some of the articles the presence of certain comorbidities, such diabetes, was obtained from reviewing medical notes. These data sources are summarised in Table 4.2. Timing within which the information on comorbidity was captured varied between studies and ranged from pre-cancer diagnosis only (up to a maximum of 5 years prior to cancer diagnosis) to pre- and post-cancer diagnosis (up to 6 months after cancer diagnosis).

Table 4-2 Data sources of comorbidity information for colorectal cancer patient cohorts

Data source	Data type	Examples
Primary care data	Routinely collected administrative data	- Medicare claims data of patient consultations with physicians (United States)
Secondary care data (e.g. hospital admissions records)	Routinely collected administrative data	- Hospital Episode Statistics (England) - Medicare claims data of hospital admissions (United States)
Diagnostic testing / examination	Ad hoc, collected for specific purpose	- Blood tests for diabetes - Recording of weight and height for Body Mass Index / obesity
Pharmaceutical prescription medicine purchases	Routinely collected administrative data	- Register of Medicinal Product Statistics (Denmark)
Medical notes	Record of patient medical history and care with one healthcare provider	- Data from specialist clinics or centres

Objective 2 – National prevalence in England

Within the literature, the availability of information on the prevalence of the thirteen conditions of interest in the general population was variable (Appendix Table 2).

Prevalence information was directly available from government agency resources (Public Health England, PHE) for six conditions: diabetes, CHF, obesity, dementia, renal disease (but only for moderate or severe chronic kidney disease) and hypertension. For some conditions, the only available information on prevalence was for a certain aspect of that condition rather than the general condition. For example, information was available for stroke (one aspect of CVD), peripheral arterial disease (peripheral vascular disease) and rheumatic arthritis (a rheumatological condition). Information on the incidence (but not prevalence) of liver disease, based on hospital records, was available from the PHE data tools website.[144]

Information on the prevalence of COPD[145, 146] and the incidence of (but not prevalence of people with a history of) MI[147] was available within the scientific literature. In addition, the scientific literature provided prevalence information on obesity,[148] dementia,[149] CHF,[150] symptomatic peripheral arterial disease (PVD)[151] and certain rheumatological conditions.[152, 153] No information was found from government sources, the grey literature or the scientific literature on the national prevalence of hemiplegia or paraplegia.

PHE prevalence information data sources were generally from: a) the National Health Service's Quality and Outcomes Framework (QOF);[154] or b) the Health Survey for England (HSE)[155] (Table 4.3).

National prevalence information in the scientific literature was ultimately sourced from the HSE or primary care sources. Primary care databases included the Clinical Practice Research Datalink (CPRD)[156] and the Royal College of General Practitioners Research and Surveillance Network (RCGP RSC).[157]

Table 4-3: Data sources of national prevalence information for England or the United Kingdom

Data from which prevalence was derived	**Data source and description**	**Information source** (depending on the condition)
Quality and Outcomes Framework (QOF)	Primary care – health indicators derived from data supplied by participating General Practices.	**Government web-based sources**: - Public Health England - NHS England
Health Survey for England (HSE)	Annual cross-sectional survey focusing of several aspects of health. Nationally representative sample selected based on residential postcode.	**Government web-based sources**: - Public Health England - NHS Digital **Scientific literature**
Clinical Practice Research Datalink (CPRD)	Primary care data – completed by a network of General Practices across the UK	**Grey literature**: - National Chronic Kidney Disease Audit$^{\pm}$ **Scientific literature**
Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC)	Primary care data collected from over 1,700 General Practices across England and Wales	**Scientific literature**
International Diabetes Federation Atlas	Four unspecified UK data sources	**Grey literature**: - Organisation for Economic Co-operation and Development (OECD) report
The Health Improvement Network (THIN)*	Primary care data – database of longitudinal patient records of approximately 6% of the UK population	**Scientific literature**
Hospital Episode Statistics (HES)$^{\lozenge}$	Routinely collected administrative secondary care data	**Government web-based sources**: - Public Health England **Grey literature**: - British Heart Foundation **Scientific literature**
English Longitudinal Study of Ageing^{+}	Multi-wave prospective cohort study of a sample of people aged 50 and over living in England (sample selected from three years of HSE samples)	**Scientific literature**
Whitehall II Study*	Multi-wave prospective cohort study, sample of UK participants aged between 35-55 years at time of recruitment to study	**Scientific literature**

$^{\pm}$Reported prevalence of moderate to severe chronic kidney disease; *Provided information on the prevalence of peripheral arterial disease;

$^{\lozenge}$ HES provided information on incidence but not prevalence of liver disease and myocardial infarction;

$^{+}$Provided information on the prevalence of dementia among people aged 50 years and over;

Abbreviations: NHS – National Health Service

Results

Data analysis: prevalence of the thirteen health conditions among the England cancer registry cohorts

Among the England cancer registry cohorts of colorectal cancer, lung cancer and Hodgkin lymphoma patients, the prevalence of comorbidity (having one or more of the conditions of interest) increased with age and with increasing deprivation (Table 4.4). There was little difference in comorbidity prevalence between males and females, although prevalence was slightly higher among males in each cohort.

In the six-year period prior to cancer diagnosis, hypertension, COPD, diabetes, CVD, CHF and PVD were among the most commonly recorded health conditions in hospital records (Appendix Table 3). The three most prevalent conditions in all three of the cancer patient cohorts were hypertension, COPD and diabetes. The age-sex adjusted prevalence of hypertension was highest in lung cancer patients – approximately 19% (18.7%; 95%CI: 18.1%, 19.2%) - and lowest in HL patients at approximately 15% (15.2%; 14.3%, 16.1%). Lung cancer patients also had a higher adjusted prevalence of COPD than the other cancer patient cohorts: 24.6% (23.6%, 25.6%), versus a prevalence of around 10% in patients with colorectal cancers or HL. Diabetes was prevalent in 5.4% (5.1%, 5.7%) of lung cancer patients, with similar adjusted prevalence across the other two cohorts of cancer patients. The adjusted prevalence of each of liver disease, obesity, CVD, renal disease, MI, CHF, PVD and of rheumatic conditions was approximately 1.5-3.0%, while the prevalence of dementia or of hemiplegia / paraplegia was lower (<1.0%).

Prevalence of chronic health conditions among colorectal cancer patients

The crude prevalence of each of the thirteen conditions of interest among the England cancer registry colorectal cancer patient cohort, and the prevalence of these conditions among colorectal cancer patient cohorts described in the scientific literature is shown in Figure 4.1. The prevalence reported in the scientific literature is illustrated according to the data source(s) from which it came: hospital records, hospital and primary care records, hospital and pharmaceutical records, clinic medical notes, diagnostic testing / physical exam, or via Medicare claims records (either hospital records only or hospital and physician records).

As would reasonably be expected, the prevalence of conditions reported tended to be higher where information was obtained from multiple sources, such as hospital records plus primary care data. This was the case for almost all of the conditions, excluding obesity. The prevalence of obesity assessed from physical exam (measuring of body mass index) was 25%, while it was less than 5% based upon hospital records or information sourced from Medicare claims-based hospital and physician records. The widest variation in prevalence reported for one condition was for hypertension: one study of patients aged ≥65 years reported 76% of patients were hypertensive, while the crude prevalence among the England cancer registry cohort of patients was approximately 40%, and the prevalence was less than 15% in a study where presence of hypertension was ascertained via testing. The reported prevalence of conditions such as dementia and hemiplegia or paraplegia was low among colorectal cancer patients, and this varied little between the data sources.

There were eleven articles reporting diabetes prevalence among colorectal cancer patients, and between them these articles covered several of the data sources. The highest prevalence among cohorts of colorectal cancer patients was from hospital and primary care records combined (approximately 24%), and from clinic medical notes (approximately 22%). By contrast, among the cohort of England cancer registry colorectal cancer patients, the crude prevalence was approximately 10%.

National prevalence of chronic health conditions in England

There were variations in the reported prevalence of hypertension, diabetes, obesity and renal disease among the general population (Figure 4.2, Appendix Table 2). The reported prevalence of obesity (26%, according to the HSE[158] and ~24% in males or females according to the scientific literature[148]) and renal disease (4.0-6.0% according to the HSE,[159] National Chronic Kidney Disease Audit (information sourced from CPRD)[160] and QOF[161, 162]) was higher than the age-sex prevalence estimated among the England cancer registry patient cohorts. The reported prevalence of hypertension varied according to the source (13.9% according to the QOF[163] while the expected prevalence per total population was estimated as 23.6% using QOF and Health Survey for England data[164]). The adjusted prevalence of hypertension among each of the three England cancer registry patient cohorts fell somewhere between these two estimates, the most similarity being between the HL patient cohort and the lower of the two general population estimates. The reported prevalence of diabetes in the general population varied from 5% to almost 7% based on source (QOF[165] or International Diabetes Federation Atlas / OECD report,[166] respectively), the former estimate being closest to the adjusted prevalence estimates within the England cancer registry patient cohorts.

The prevalence of COPD or CHF among each of the England cancer registry cohorts was higher than that reported in the general population. In primary care sources (RCGP RSC) the prevalence of COPD was reported as ~2.6%[146] and based on data from the HSE, the expected prevalence was 3.5%.[145] The prevalence of CHF in the general population was 0.8% according to the QOF[167] or 1.4% according to primary care data (CPRD),[150] and ranged from 2.5% (2.3%, 2.8%) in lung cancer patients to 1.4% (1.4%, 1.5%) of colorectal cancer patients.

According to CPRD / QOF, the reported prevalence of dementia was 4.3% of people aged 65+ years in England[164] (not shown in Figure 4.2), while data obtained from the English Longitudinal Study of Ageing estimated that approximately 767,000 people in England and Wales had dementia[149] (i.e. about 1.3% of this population). The adjusted prevalence of dementia among each of the three England cancer

registry cohorts was <1%. There was no information directly available for the prevalence of CVD or rheumatological conditions among the general population in England.

Discussion

Hospital admissions records were used to derive the prevalence of thirteen chronic health conditions among three England cancer registry cohorts of patients in the six-year time window prior to their cancer diagnosis. The work undertaken in this section of the thesis aimed to evaluate the use of hospital records for capturing information on chronic disease prevalence. This was investigated in two ways: firstly comparing the crude prevalence of the thirteen conditions among the England cancer registry cohort of colorectal cancer patients with the prevalence of these conditions among cohorts of colorectal cancer patients described in the scientific literature, and secondly comparing the age-sex adjusted prevalence of the conditions among the England cancer registry cohorts of colorectal cancer, lung cancer and Hodgkin lymphoma patients with the reported prevalence of these conditions among the general population in England. This allowed insight into alternative sources of information on chronic disease prevalence.

Comorbidity among colorectal cancer patients

Among the studies retrieved from the literature review, hospital data were commonly used as a source of information of cancer comorbidity, either independently or with primary care (i.e. General Practice / physician) data. Patterns in terms of the conditions most prevalent among colorectal cancer patients were fairly consistent where comorbidity information was captured from these data sources. Hypertension, COPD and diabetes were the three most common conditions based on retrospective cohort or cross-sectional studies using these routine administrative data sources. The variation in prevalence of certain conditions may be due to these conditions being underreported in hospital data.

Less severe comorbidities, such as obesity, may be underrepresented in hospital data of older patients and in patients with more severe comorbidities, due to competing demands from other health conditions requiring clinical treatment. Diabetes may also be underreported in hospital records as it can be well managed through primary care.[168]

In comparison with the prevalence information I obtained using the HES data, the prevalence of many of the conditions, such as COPD, CHF, PVD and rheumatological conditions tended to be higher where hospital data were used in conjunction with primary care data. However, comparisons between the colorectal cancer patient cohorts should be drawn with extreme caution. Due to heterogeneity in patient characteristics of the different cohorts of colorectal cancer patients in these studies, and differences in the timeframes within which information on comorbidity was considered relative to time of cancer diagnosis, it cannot be assumed that differences in prevalence are solely due to differences between data sources of information on comorbidity. For example, information on comorbidity prevalence available from Medicare claims from hospital and / or physician appointments represents comorbidity among patients aged 65 years and above, i.e. people who are eligible for Medicare health insurance. It is generally anticipated that the prevalence of comorbidity would increase with increasing age,[14] so cohorts of older cancer patients would have a higher prevalence of comorbidity than cohorts of adult patients of all ages.

Chronic disease in the general population

This study highlighted a lack of available information on the national prevalence of some health conditions in England. Where information on a condition was available from multiple sources, there was sometimes inconsistency between the sources. These findings were unexpected.

Much of the available information was sourced from the Health Survey for England (HSE) or the Quality of Outcomes Framework (QOF). The HSE began in 1991 and is completed annually, with participants

selected to be nationally representative of people living at private addresses. Between the period 1994 to 2009, the annual estimated adult interview response rate ranged from 58% to 75%.[169] The QOF was introduced in 2004, and provides reward and financial incentive to volunteering general practices for the quality of care they provide to patients.[154] Up to 25% of general practitioners' income is linked to the achievement of quality targets for several chronic conditions. Such financial incentives may benefit patients with the relevant conditions, but might also be detrimental to patients with other conditions or for whom quality targets are seen as more difficult to achieve.[170] Whether the design and participation of both the HSE and QOF are optimal for capturing information on the national prevalence of a broad range of health conditions is not clear. Both are open to sources of potential bias. Financial incentive could influence the reporting for the QOF. With the HSE, non-response bias could occur if the characteristics of those invited but not participating were different from those that participated, while data collected from survey questionnaires is liable to responder bias.[171] Systematic registration has been implemented for some of the conditions of interest, such as diabetes, in countries like the United States and Sweden, although this practice does not occur in the UK.

I estimated the prevalence of thirteen chronic health conditions among three cohorts of cancer patients in England from well-established data sources: cancer registration data linked with HES. I hypothesised that, of the three cohorts of patients, the prevalence of conditions among the HL patient cohort would be the most similar to the reported prevalence among the general population, given that HL traditionally has an infectious rather than environmental or behavioural aetiology. I expected that the prevalence of some chronic conditions would be higher in the other two cancer patient cohorts than in the general population, particularly where cancer and chronic condition share common risk factors. For example, as tobacco smoking is strongly associated with developing both lung cancer[118] and COPD,[172, 173] we assumed COPD prevalence would be higher among this cohort of cancer patients. Likewise, we would expect both diabetes and obesity to be highly prevalent among colorectal cancer patients, as both conditions share similar risk factors with colorectal cancer,[174 175] and diabetes is in itself a risk factor for colorectal cancer.[31] The reported prevalence of renal disease

(moderate to severe chronic kidney disease) among the general population was 3-4% higher than the prevalence among the cancer patient cohorts. The sources of general population prevalence were the HSE, a Chronic Kidney Disease Audit report and the QOF. The lower prevalence of renal disease among pre-diagnosis cancer patients, obtained from hospital data, may be reflective of certain patients electing not to receive treatment (such as dialysis) for this condition. For example, untreated kidney failure appears to be more common among older people.[176]

Using hospital data as a source of information on comorbidity

It would have been useful to have more than one source of information on comorbidity for the cancer patients we studied, in order to compare the prevalence obtained using hospital data with prevalence information from alternative sources for the same study population. Studies conducted outside of the United Kingdom comparing available information from different data sources have considered medical charts to be the 'gold standard' of information on comorbidity. Two Australian studies comparing administrative hospital data with clinical medical charts found the prevalence of some comorbid conditions studied to be lower in hospital administrative data versus medical charts.[132, 177] In similar studies conducted in Singapore,[178] Canada[179, 180] and the United States[181] the results were more mixed, some conditions were better recorded in the hospital charts while others were more prevalent based on information from hospital administrative data. The underreporting of some conditions in the administrative data, as compared with hospital medical charts, may arise as comorbidity is less important to report for hospital admission than for any complications arising while the patient is in hospital.[132] Moreover, one of the Australian studies was investigating comorbidity among patients with heart disease. The importance of capturing information on specific comorbidities may vary according to the primary disease being treated, for example, placing priority upon reporting the presence of comorbid conditions that may interact with the primary disease to cause adverse

patient outcomes. Additionally, as previously discussed, recording of certain comorbid conditions may take priority over others, based upon the severity of the condition.

There are some limitations with using hospital records for estimating the prevalence of chronic health conditions. The information available is limited to conditions diagnosed during a time of hospital visit. In addition, information derived from the diagnostic fields of the hospital records may be subject to measurement error and misclassification, arising either during collation or during the coding of information. In England, the Hospital Episode Statistics (HES) database of admissions at National Health Service hospitals incorporates both clinical information about diagnoses and operations and administrative information such as dates and methods of admission.[71] The coding of clinical diagnoses, including comorbidities, is undertaken by highly trained clinical coders, but these coders are working independently from front line clinicians often using unstructured and unstandardized clinical notes.[182] It is unclear exactly what impact this may have on the level of detail extracted from the notes from medical charts, and the integrity of the information transferred to the HES records. A study in England using data from the Clinical Practice Research Datalink (CPRD) primary care database linked with HES secondary care data reported that, based on the comorbid conditions of the Charlson Index, more comorbidity was recorded in primary care data than secondary care data. With the exception of metastatic solid tumour and hemiplegia, the recorded prevalence of each of the Charlson Index conditions was higher based upon primary care data than secondary care data.[183] However, the CPRD database covers approximately 7% of the UK population[184] while the HES database contains all admissions, A&E attendances and outpatient appointments at NHS hospitals in England.[185] For the data used in our study, the linkage between cancer registry data and HES data was over 99%. Moreover, we assumed that the more severe conditions will require medical assistance in a hospital and will be documented in patient records.

When drawing comparisons between countries in respect to the recording of chronic diseases in hospital records, differences between healthcare systems in terms of the procedures for diagnosing and managing these conditions should be acknowledged. In the UK, the healthcare system is designed so that most investigations and diagnostic procedures are performed within the National Health Service hospitals, where patients attend the hospital as an outpatient following a referral to a specialist. In the UK, specialists work in the secondary care setting while in many other countries, specialist doctors are numerous within primary care, and investigations may be made in that setting, without the need for the patient to visit a hospital. Therefore, in theory, comorbidities should be well captured from UK hospital records relative to comorbidities captured from hospital records in these other countries.

An advantage of using population-based administrative data sources to capture information on cancer comorbidity is their generalisability, and their low cost relative to other methods of data collection.[131] The prospective cohort studies of colorectal cancer patients retrieved from the literature search used testing or physical examinations at the time of enrolment to ascertain the presence of the chronic health conditions. Such studies may offer more opportunity and flexibility in respect to the type and scope of data collected, but can be costly and time consuming to undertake.[131] In a similar way to prospective cohort studies, cancer patient clinical trial data may provide detailed information on participants, including information on their comorbidities. However, older patients and patients with comorbidity have been historically underrepresented in cancer clinical trials,[186] which compromises the extent of the generalisability of these data. No studies of comorbidity among colorectal cancer clinical trial patients were found during the search of the literature. Cancer registration databases do not commonly include information on patient comorbidities due to limitations in the scope of the data that can be collected. However, many cancer registries endeavour to collect information on comorbidities that are relevant for the patient care through linkage with other clinical datasets.[187]

From our data sources, we were able to investigate the prevalence of comorbidities in over 300,000 cancer patients in England. The benefit of a large study population is that it improves the stability of prevalence estimates, particularly in the case of rarer conditions.[188]

There was limited information on the national prevalence of the conditions that we investigated, with which to compare the prevalence estimates obtained from HES. Additionally, the prevalence of some cancer comorbidities was higher when information was sourced from a combination of primary care and secondary care data. Nonetheless, from the hospital data we used we were able to establish that, according to type of cancer, between 30-67% of the cancer patients we studied had at least one recorded comorbidity. These data can inform further research into the influence of comorbidity on cancer outcomes. Within epidemiological studies in the scientific literature, hospital admissions data are a widely used source of information on cancer comorbidity. Although some health conditions could be under-recorded or under-reported within these data, this only serves to highlight that the burden and consequences of comorbidity on cancer patient outcomes may be underestimated.

Table 4-4: Characteristics of patients aged 15-90 years diagnosed with colorectal cancer, lung cancer or Hodgkin lymphoma in England between 2009 and 2013

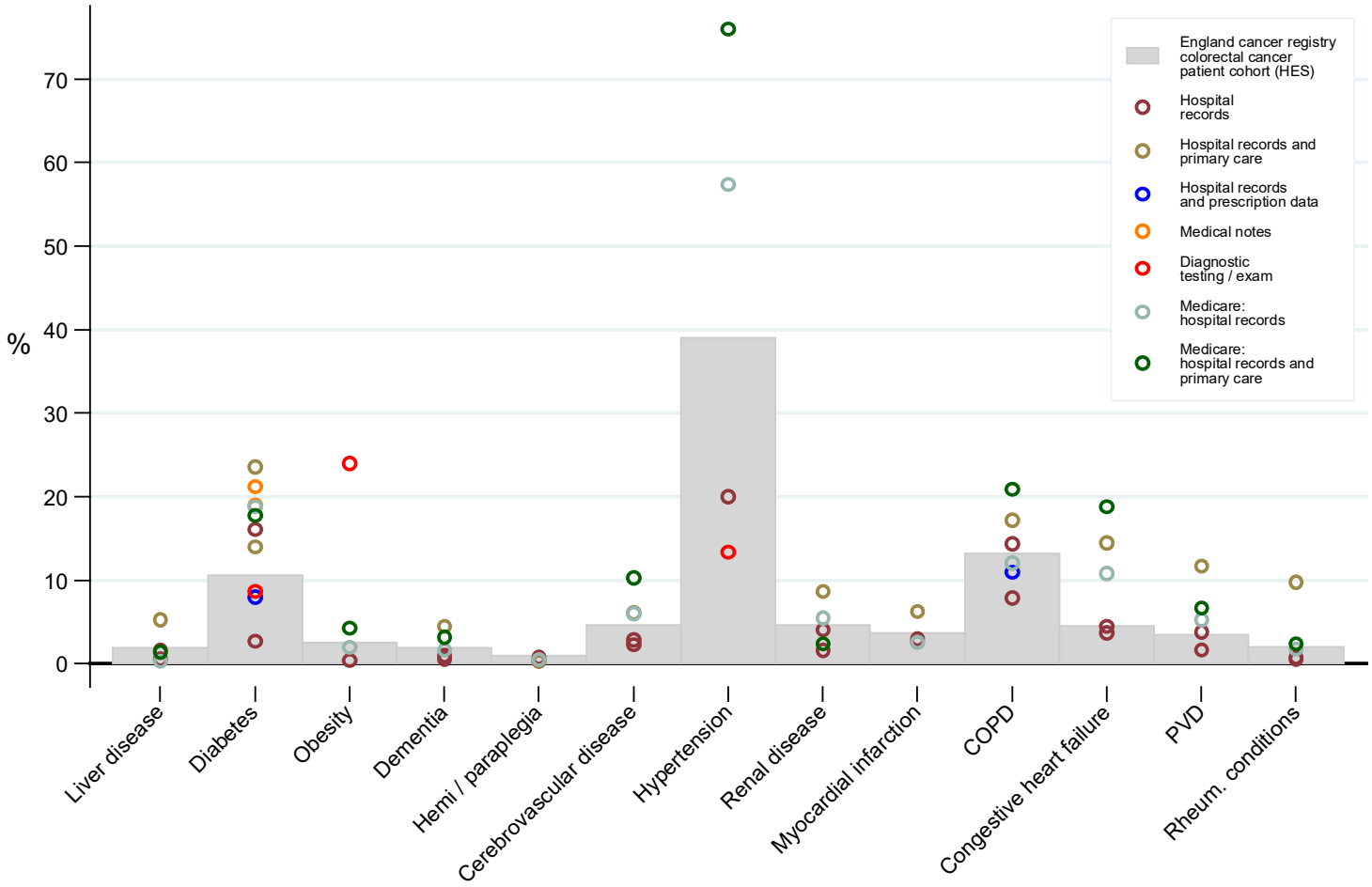
	Colorectal				Lung				Hodgkin lymphoma			
	All patients		Patients with comorbidity		All patients		Patients with comorbidity		All patients		Patients with comorbidity	
	N	%*	n	%**	N	%*	n	%**	N	%*	n	%**
Sex												
Male	90,055	56.8	47,818	53.1	91,568	55.3	62,235	68.0	4,163	56.1	1,256	30.2
Female	68,503	43.2	36,120	52.7	74,109	44.7	49,448	66.7	3,257	43.9	950	29.2
Age (years)												
15-29	976	0.6	135	13.8	178	0.1	58	32.6	2,111	28.5	226	10.7
30-44	4,218	2.7	765	18.1	1,757	1.1	545	31.0	1,660	22.4	248	14.9
45-59	21,568	13.6	6,390	29.6	19,923	12.0	9,155	46.0	1,461	19.7	460	31.5
60-74	67,396	42.5	32,627	48.4	75,085	45.3	49,112	65.4	1,398	18.8	747	53.4
75-90	64,400	40.6	44,021	68.4	68,734	41.5	52,813	76.8	790	10.6	525	66.5
Deprivation (IMD income)												
Least deprived	34,290	21.6	16,587	48.4	23,066	13.9	14,477	62.8	1,339	18.0	359	26.8
2	34,845	22.0	17,551	50.4	28,411	17.1	18,498	65.1	1,428	19.2	415	29.1
3	33,341	21.0	17,662	53.0	32,822	19.8	21,842	66.5	1,462	19.7	444	30.4
4	31,206	19.7	17,442	55.9	39,220	23.7	26,864	68.5	1,618	21.8	486	30.0
Most deprived	24,876	15.7	14,696	59.1	42,158	25.4	30,002	71.2	1,573	21.2	502	31.9
TOTAL	158,558	100.0	83,938	52.9	165,677	100.0	111,683	67.4	7,420	100.0	2,206	29.7

Abbreviations - IMD: Indices of Multiple Deprivation;

*Percentage of patients with cancer type

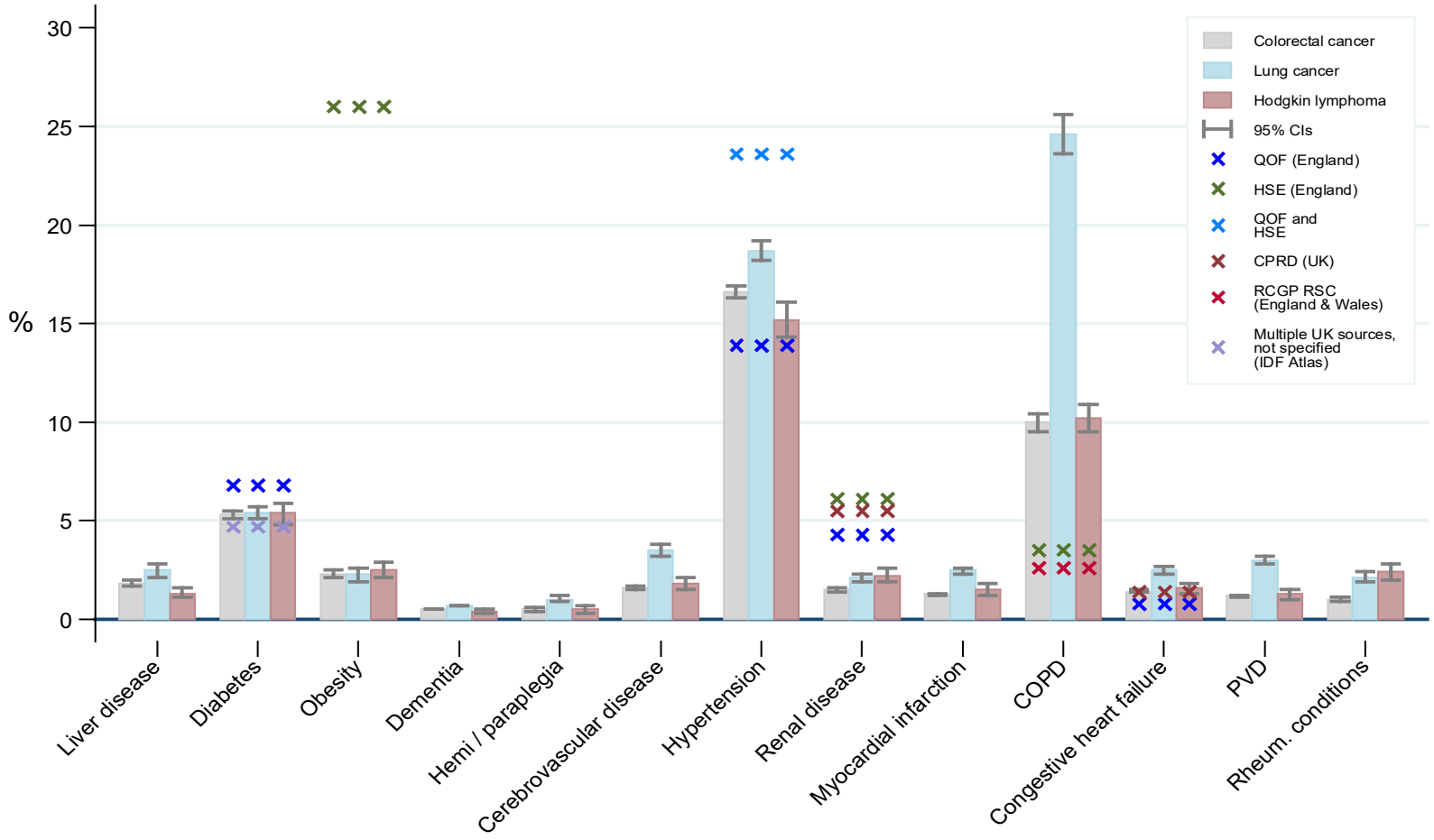
** Percentage according to patient characteristic and cancer type

Figure 4-1: Prevalence (%) of thirteen comorbidities among the England cancer registry cohort and among colorectal cancer patients reported in the scientific literature



NOTE: The prevalence reported for each cohort is the percentage of patients with the respective condition
Prevalence among cohorts in the scientific literature presented according to data source
Abbreviations
COPD - Chronic obstructive pulmonary disease; HES - Hospital Episode Statistics; PVD - Peripheral vascular disease; Rheum - Rheumatological

Figure 4-2: Prevalence (%) of chronic conditions among the three England cancer registry cohorts and among the general adult population in England / UK



NOTE: Prevalence reported for the England cancer registry cohorts is the age-sex adjusted prevalence with 95% confidence intervals (prevalence information sourced from Hospital Episode Statistics data)
General population prevalence reported by data source
Abbreviations
COPD - Chronic obstructive pulmonary disease; CPRD - Clinical Practice Research Datalink; CI - Confidence interval; HSE - Health Survey for England;
IDF - International Diabetes Federation; PVD - Peripheral vascular disease; QOF - Quality and Outcomes Framework; Rheum - Rheumatological;
RCGP RSC - Royal College of General Practitioners Research and Surveillance Centre; UK - United Kingdom

Fulfilment of the second objective of this thesis

The study described in Research Paper 2 investigated the prevalence of fourteen comorbidities among population-based cohorts of cancer patients and showed that the most deprived groups of patients carried the greatest burden of comorbidity and multiple comorbidity. While it is acknowledged that comorbidity in general terms can influence cancer prognosis, it would be useful to understand whether certain conditions have a greater influence that others on the poorer short-term prognosis experienced by the most deprived groups of cancer patients.

The study I described in the second part of this chapter aimed to evaluate the measurement of comorbidity and the use of hospital data for this purpose. The findings from this study suggested that some conditions may be underreported in hospital data, and that access to additional sources of data (such as primary care data) to compliment hospital data may allow a more complete picture of cancer comorbidity. Nonetheless, the English hospital data provide a population-based insight into common comorbidities, and an indication of the (minimum) burden of comorbidity, among cancer patients.

The most common conditions among the cohort of colon cancer patients were COPD, diabetes, hypertension, and cardio-vascular conditions such as CHF, MI, PVD and CVD. The age-sex adjusted prevalence of diabetes among the colon cancer patients was similar to the prevalence reported among the general population in England, while the age-sex adjusted prevalence of COPD among colon cancer patients was higher than the prevalence among the general population. Socio-economic deprivation was associated with the presence of each of the common conditions among colon cancer patients. In the next chapter of my thesis I investigate whether time living with COPD, diabetes or the cardio-vascular conditions and frequency of hospital admissions prior to cancer diagnosis are an explanatory factor in the socio-economic inequalities in ninety-day mortality described in Chapter 3.

Chapter 5 - The role of time with comorbidity and timing and duration of hospital admissions pre-cancer diagnosis on socio-economic inequalities in short-term colon cancer mortality

This chapter describes the research study undertaken to achieve the third objective of this thesis: to investigate whether timing of comorbidity and timing and duration of hospital visits pre-cancer diagnosis influence socio-economic inequalities in short-term colon cancer mortality. This work has been written up as a research article for peer-review publication. The chapter includes the background, description, main findings and conclusions of the study, a copy of the manuscript and a summary of how this work fulfils the third objective of the thesis.

Introduction to research paper 3

Background

The study of prognostic factors influencing socio-economic inequalities in ninety-day mortality (Research paper 1)[101] showed that comorbidity was a strong prognostic factor of ninety-day mortality among colon cancer patients. It also showed that socio-economic inequalities in ninety-day mortality were wider among patients with comorbidity than among patients with no recorded comorbidity. My study of comorbidity prevalence among cancer patients (Research paper 2)[127] showed that the most deprived colon cancer patients tend to carry a greater burden of comorbidity. To further evaluate the role of comorbidity in socio-economic inequalities in ninety-day mortality, the next step of the research conducted for this thesis was to investigate comorbidity in more detail. Rather than use a summary metric of comorbidity, I focused on specific comorbidities that were either notably prevalent

among colon cancer patients or were a known risk factor for mortality. The impact of pre-existing comorbidities on patient health may be influenced by the time since the comorbidity first occurred and on the cumulative effect of living with the condition over a period of time. To investigate this further, I investigated time living with specific comorbidities prior to cancer diagnosis and hospitalisations occurring during this time, which I considered as time-varying proxy measures of the severity of the comorbidity and patient health status. An earlier study of comorbidity (not specific to a primary disease) as a prognostic factor in patient mortality concluded that models incorporating measures of duration, recency and severity of comorbidity offered a better model fit than models only including the presence of comorbidity.[189]

The aim of this study was to investigate socio-economic inequalities in ninety-day mortality among colon cancer patients with comorbidity, and examine whether the time-varying proxy measures of comorbidity severity, plus other prognostic factors, explain some of the differences in the risk of short-term mortality between the most and least deprived patients. My hypothesis was that patients with longer-term pre-existing comorbidities and more frequent hospital admissions (i.e. greater comorbidity severity) would be more at risk of dying within ninety days of colon cancer diagnosis.

The three comorbidities studied were diabetes, chronic obstructive pulmonary disease (COPD) and the cardio-vascular conditions of the Charlson Comorbidity Index (CCI)[83] – myocardial infarction or congestive heart failure, cerebrovascular disease and peripheral vascular disease. These comorbidities were selected due to their prevalence among the cohort of colon cancer patients[127] and because their presence may impact upon mortality among colorectal cancer patients.

Some risk factors for developing Type 2 diabetes are similar to those for developing colon cancer, i.e. poor diet,[122] lack of exercise[122] and tobacco smoking.[190] Diabetes may also develop due to non-

modifiable risk factors such as genetic predisposition[191] and ethnicity.[192] Adverse outcomes among patients with diabetes are more common among male patients and older patients,[193] and among those of lower socio-economic position.[194] Diabetes can increase the risk of cardiovascular events and mortality,[195, 196] including increasing mortality risk among colon cancer patients.[197-199]

Tobacco smoking remains, so far, the predominant factor in the aetiology of COPD; other factors include exposure to air pollution, occupational hazards and infections.[200] Auto-immunity may also have an indirect contribution: pulmonary damage caused by tobacco smoking or other environmental toxins can produce auto-immunological reactions that ultimately lead to the development of COPD.[201] There is evidence that women are more likely to have unfavourable clinical expression and adverse outcomes from COPD than men, [202, 203] while lower socio-economic position can contribute towards earlier mortality among patients with COPD.[204]

Common risk factors for developing cardio-vascular diseases include tobacco smoking, obesity and an abnormal level of cholesterol and other lipids in the blood.[205] The prevalence of,[206] and mortality from,[207] cardio-vascular conditions tends to be higher in men than women. Mortality from cardio-vascular conditions is also associated with lower socio-economic position[208] and with lifestyle factors such physical activity.[209] Cardio-vascular conditions have been shown to increase cancer-related and all-cause mortality among colorectal cancer patients. [48, 116]

Methods and materials

The data used for this study were National Cancer Registry data for England linked with electronic health records (Hospital Episode Statistics). The study population was patients aged 15-90 years who had been diagnosed with colon cancer in England between 2009 and 2013, and who had a recording of either diabetes, COPD or the cardio-vascular conditions in the Hospital Episode Statistics data in the six years prior to cancer diagnosis. Analyses were conducted separately according to whether patients

had diabetes, chronic obstructive pulmonary disease or cardio-vascular comorbidities, and the sex of the patient. These sub-groups of patients studied ranged in size from approximately 4,600 to 9,200 patients.

The first objective of the study was to estimate the socio-economic inequalities in ninety-day mortality among each of the sub-groups of patients – i.e. to estimate the difference in predicted mortality between the most and least deprived groups of patients. The second objective was to examine whether the proxy measures of severity (i.e. time since comorbidity was first recorded and frequency and duration of hospital admissions during this time), plus other prognostic factors, influenced the magnitude of the inequalities within each sub-group of patients. The proxy measures of comorbidity severity were analysed as time-varying covariates, and used to estimate the weight function of their effect of on ninety-day mortality using Weighted Cumulative Exposure (WCE) models.[210] These models have commonly been used in the pharmaco-epidemiology setting, and weight information about duration, timing and intensity of an exposure and estimate the effect of this weighted cumulative exposure on the outcome of interest, while adjusting for other fixed-effect covariates. The advantage of using this approach is that it accounted for the time-varying effect of these exposure measures of comorbidity severity on the outcome. Traditional approaches to modelling these measures of exposure may require that the exposure variables are summarised, and thus time-varying information, which may be relevant to the relationship between the exposure and outcome, is lost.

Main findings

Socio-economic inequalities in ninety-day mortality varied according to the comorbidity studied and sex of the patient. Initial analyses of each sub-group of patients (adjusting for age and deprivation) showed that the widest inequalities were among female patients with COPD: the most deprived patients had a 71% increased risk of mortality compared with the least deprived patients (HR: 1.71; 95%CI: 1.42, 2.07).

Accounting for the weighted cumulative effect of the proxy measures of comorbidity exposure reduced the magnitude of the socio-economic differences in mortality among all patient groups studied. The reduction ranged from 5% to 17%: among female patients with one of the cardio-vascular conditions, the hazard ratio of ninety-day mortality of the most versus least deprived patients reduced from 1.42 (95% CI: 1.21, 1.67) to 1.37 (1.16, 1.61), while among male patients with COPD the hazard ratio of the most versus least deprived patients reduced from 1.25 (1.05, 1.48) to 1.08 (0.91, 1.28). This represented a 12% and 68% relative reduction, respectively.

There was a marked contrast in the results estimating socio-economic differences in ninety-day mortality among male and female patients with COPD, which was unexpected. Among the male patients, after adjustment for the weighted cumulative exposure measures of comorbidity, emergency presentation and the presence of multiple other comorbidities, there was no evidence of mortality differences between the most and least deprived patients (HR 1.00; 95% CIs 0.85, 1.19). By contrast, the most deprived female patients still had a 40% increased hazard of mortality compared with the least deprived group after adjusting for these same factors (HR 1.40; 1.16, 1.69).

The differences between male and female patients with diabetes or cardio-vascular conditions were less notable. Following adjustment for prognostic factors, the most deprived groups of patients with these conditions still had a 10-20% higher hazard of mortality than the least deprived groups.

Emergency presentation was strong prognostic factors of ninety-day mortality, regardless of the patient's sex, age, deprivation group or the comorbidity being studied. The presence of additional comorbidities posed a bigger hazard of ninety-day mortality to female patients than male patients.

Conclusion

The study showed that accounting for the time living with comorbidity before cancer diagnosis, and the frequency and duration of hospital admissions during that time, appeared to reduce the socio-economic differences in short-term mortality among patients with diabetes, COPD or cardio-vascular conditions. These findings suggest a differential pattern of healthcare utilisation between the most and least deprived patients, which may be due to varying severity of comorbidity, different healthcare seeking behaviours, or varying complexity of healthcare needs, for example, due to the presence of multiple comorbidities.

Fulfilment of the third objective of this thesis

In this chapter I examined ninety-day mortality among colon cancer patients with diabetes, COPD or cardio-vascular conditions. I investigated whether severity of comorbidity may influence socio-economic inequalities in ninety-day mortality, using time living with comorbidity and the frequency and duration of hospital admissions during that time as proxy measures of comorbidity severity.

Accounting for these proxy measures of comorbidity severity reduced the socio-economic differences in ninety-day mortality among patients with these comorbidities. Differences were further reduced after adjusting for cancer diagnosis via emergency presentation and the presence of multiple additional comorbidities, but the overall reduction varied according to the sex of the patient and the main comorbidity being studied.

Differential healthcare utilisation prior to cancer diagnosis may influence short-term prognosis after cancer is diagnosed. Emergency presentation was a strong prognostic factor in ninety-day mortality. Exploring the management of pre-existing comorbidities and healthcare utilisation according to deprivation group may further disentangle mechanisms behind the inequalities in short-term mortality among cancer patients with comorbidity. For example, investigating whether there are opportunities for earlier cancer diagnosis among the most deprived patients with pre-existing comorbidities that share common risk factors with cancer or are considered in themselves as risk factors for developing cancer.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Helen Fowler
Principal Supervisor	Bernard Rachet
Thesis Title	The role of comorbidity in socioeconomic inequalities in short-term mortality among colon cancer patients in England

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	International Journal of Epidemiology
Please list the paper's authors in the intended authorship order:	Helen Fowler, Dimitria Kleio Kipourou, Michal Abrahamowicz, Marie-Eve Beauchamp, Coraline Danieli, Bernard Rachet, Aurelien Belot
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of the paper. I conducted the literature review, managed the data and conducted the analysis. I prepared all drafts of the paper. The coauthors provided guidance with the design of the study and analysis strategy, and provided feedback on the

	drafts of the paper I prepared.

Student Signature: [redacted] **Date:** 16/10/20

Supervisor Signature: [redacted] **Date:** 19 October 2020

Timing and duration of hospital admissions and time with comorbidity: explanatory factors in socioeconomic inequalities in short-term mortality among colon cancer patients with comorbidity? A population-based retrospective cohort study

Helen Fowler, Dimitra-Kleio Kipourou, Michal Abrahamowicz, Marie-Eve Beauchamp, Coraline Danieli, Bernard Rachet, Aurélien Belot

Abstract

Background

The prevalence of additional chronic diseases, or comorbidities, among cancer patients is associated with increased levels of socioeconomic deprivation, while the presence of comorbidities can influence cancer outcomes. The most deprived colon cancer patients tend to have poorer short-term prognosis following diagnosis. This study investigated the influence of time-varying dimensions of comorbidity in socioeconomic inequalities in short-term mortality among colon cancer patients.

Methods

This retrospective cohort study used population-based cancer registry data of patients aged 15-90 years diagnosed with colon cancer in England between 2009 and 2013, and who had a recording of either diabetes, chronic obstructive pulmonary disease (COPD) or cardio-vascular conditions within linked Hospital Episode Statistics data in the six years prior to cancer diagnosis.

Weighted Cumulative Exposure models estimated the time-varying dimensions of timing and duration of hospital admissions and time with comorbidity (considered as proxy measures of comorbidity severity) on ninety-day mortality among subgroups of patients defined according to comorbidity (diabetes, COPD, or cardio-vascular conditions) and sex.

Results

Accounting for the time-varying dimensions of comorbidity reduced the magnitude of socioeconomic differences in mortality among each of the patient subgroups. The reduction in the hazard ratio of ninety-day mortality (most versus least deprived patients) was smallest among the female patients with cardio-vascular conditions (from HR: 1.42; 95%CI: 1.21, 1.67 to HR: 1.37; 1.16, 1.61) and largest among male patients with COPD (1.25; 1.05, 1.48 to 1.08; 0.91, 1.28), representing a 12% and 68% relative reduction, respectively. Adjusting for emergency diagnosis with colon cancer and the presence of other comorbidities reduced differences in mortality further.

Conclusions

Differential healthcare utilisation prior to cancer diagnosis may contribute towards some of the mortality differences between the most and least deprived colon cancer patients with comorbidity. However, even after accounting for this and other prognostic factors, differences in mortality among these patients remained. Further investigation of healthcare utilisation and availability of resources, stage of cancer diagnosis and options for cancer treatment may provide insights into mechanisms which lead to poorer short-term prognosis among the most deprived groups of patients with comorbidity.

Introduction

The presence of additional long-term health conditions, or comorbidities, can affect cancer outcomes.[1] Studies investigating cancer outcomes commonly evaluate the patient's comorbidity status using summary metrics of comorbidity. For example, the Charlson Comorbidity Index (CCI)[2] assigns a weighting to each condition present based upon mortality risk and provides the patient with an overall comorbidity score. While these metrics offer an overall snapshot of comorbid conditions present (and can give an indication of comorbidity severity, based on weightings assigned to conditions), they are not informative in respect to the length of time the patient has lived with these conditions, and how these conditions may have impacted the patient's health historically in the time before their cancer diagnosis.

Patient performance status is a measure of health status used in epidemiological research. It is a score that defines a patient's ability to perform certain activities of daily living, and is used by clinicians to determine the best treatment options for patients.[3] Performance status is considered a prognostic factor for many cancers, such as non-small cell lung cancer,[4] but is representative of health status at a given point in time.

The existence of socioeconomic inequalities in short-term colon and colorectal cancer outcomes is well acknowledged in the scientific literature, the more deprived groups of patients having worse outcomes, even after adjusting for age, stage at diagnosis and other prognostic factors.[5-8] The more deprived groups of patients tend to carry most of the burden of comorbidity or multimorbidity.[9-12] It has been established that the presence of comorbidity can influence options for care following the patient's cancer diagnosis, for example, it can have an impact on whether a patient receives curative cancer treatment.[1] Some comorbidities have been linked with complications[13] and higher Intensive Care Unit (ICU) admission[14] among post-operative cancer patients. Comorbidity can also be predictive of duration of hospital stay following cancer diagnosis.[15]

The aim of this study was to investigate factors that may influence socioeconomic inequalities in ninety-day mortality among colon cancer patients with comorbidity, accounting for the timing and the duration of comorbidities and hospital admissions. The study focused on three comorbid conditions, selected because of their noticeable prevalence and their general impact on risk of death. Firstly, diabetes, which is a known risk factor for the development of colon cancer[16] and mortality among patients with colon cancer.[17-21] Secondly, chronic obstructive pulmonary disease (COPD), which was found to be one of the most prevalent conditions of the CCI among colon cancer patients in a descriptive study of cancer comorbidity in England.[9] Lastly, we investigated the cardio-vascular conditions of the CCI (history of myocardial infarction or congestive heart failure, cerebrovascular disease and peripheral vascular disease), given that cardio-vascular diseases are a common cause of mortality[22] and can increase mortality risk among colorectal cancer patients.[23, 24] We considered time with the comorbidity and timing and duration of hospital admissions while living with the comorbidity as proxy measures of comorbidity severity and health status, and our objective was to investigate whether these measures, plus other prognostic factors, explain some or all of the inequality in short-term prognosis between the most and least deprived patients.

Methods

Data

This study uses national cancer registry data linked with hospital admissions records (Hospital Episode Statistics,[25] 'HES'), Route to Diagnosis data,[26] and national bowel cancer clinical audit data[27] ('NBOCA' – data compiled by clinicians and other health care professionals working with patients in hospitals in multi-disciplinary teams). Data were of patients aged between 15-90 years, diagnosed with cancer of the colon in England between 2009 and 2013. Patients over the age of 90 years were excluded due to a combination of factors: their shorter life expectancy, the association between higher prevalence of comorbidity and increased overall mortality among very elderly patients,[28] and because treatment options among this age group may differ from those of younger patients, particularly among patients with comorbidity, due to an increased risk of post-operative complications.[29] Information on diagnosis date, age at diagnosis, vital status, date of last follow up, patient sex, socioeconomic deprivation group (based on patient residential postcode at time of diagnosis, and defined according to the deprivation quintiles of the Income domain of the Indices of Multiple Deprivation[30]) were obtained from registry data. The HES data provided information on timing and duration of hospital admissions occurring up to six years prior to cancer diagnosis, and information on the presence and timing of health conditions (the comorbidities), based upon the diagnostic fields and admission dates within the data. Route to Diagnosis data indicated the channel through which the colon cancer had been diagnosed. Information on cancer stage at diagnosis in these data was obtained from the clinical audit data and registry data. The stage variable was a composite variable based on the TNM classification system[31] and derived using an algorithm prioritising information on stage from multiple sources.[32]

The data were in longitudinal format, with each observation representing a one-month interval of the time from six-years prior to cancer diagnosis (the comorbidity look-back period) to the three months of follow-up after cancer diagnosis. Thus, the exposure and outcome were captured in separate time-

intervals within the data. Figure 1 provides an illustration of the design of our study, with three examples of patient scenarios.

Analyses were conducted separately on six sub-groups of patients that were based on patients with the comorbidities of interest (i.e. diabetes, COPD or cardio-vascular conditions) and the sex of the patient.

Outcome

The outcome of interest in this study was mortality within ninety days from colon cancer diagnosis. This was measured as a binary variable, indicating the patient's vital status (alive or dead) at ninety days from the date of diagnosis.

Exposure (proxy measures of comorbidity severity)

For each of the comorbidities of interest, the time-varying exposure variable captured the duration of hospital admissions occurring during each monthly time-interval prior to cancer diagnosis, defined in terms of the number of "bed days" (i.e. the total number of days of the hospital admission or spell, from the admission date to the discharge date). Thus, based on the time-interval, this variable also defined when the comorbidity was first recorded, and the timing of when the hospital admissions occurred. Appendix Table 1 provides an illustration of how this variable is defined in our data, based on the hypothetical patient scenarios presented in Figure 1.

Other covariates

In addition to the deprivation group variable, other covariates (all being time-fixed) included age at diagnosis, whether or not the patient had been diagnosed with colon cancer via emergency

presentation, and whether the patient was also living with additional comorbidities to the one being investigated as the main exposure. Depending on main comorbidity being studied, other additional comorbidities included: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatological conditions, liver disease, diabetes, hemiplegia or paraplegia, renal disease, obesity or hypertension.

The assumed causal relationships between the variables, time with comorbidity, and ninety-day mortality are depicted in the directed acyclic graph in Appendix Figure 1. The relationships are defined at the time of cancer diagnosis. As the most deprived patients tend to carry a greater burden of comorbidity and multiple comorbidity,[9] and comorbidity is more prevalent in older patients,[12] time with comorbidity and the presence of other (multiple) comorbidities were assumed to be associated with both deprivation and age. Emergency presentation with colon cancer was also considered to be associated with age and deprivation,[33] and also a more advanced stage at diagnosis.[34]

Analysis

Cross tabulations were used to summarise i) the distribution of patient characteristics and ii) time with comorbidity and total duration of time spent in hospital according to the comorbid conditions being investigated.

Weighted Cumulative Exposure models

We used weighted cumulative exposure (WCE) models in order to account for the dimensions of our exposure variable representing comorbidity severity (i.e. the time since the comorbidity of interest was first recorded, the timing of hospital admissions and the number of bed days spent in hospital during the admission). We considered the number of bed days as an indicator of the intensity of the comorbidity. WCE models, proposed by Sylvestre and Abrahamowicz,[35] weight information about

duration, timing and intensity of the exposure, and estimate the effect of this weighted cumulative exposure on the outcome of interest, while adjusting for other fixed-effect covariates. In our analyses the time-to-event process (from the time of cancer diagnosis to ninety-days following cancer diagnosis) was modelled using the Cox proportional hazards model.

The purpose of using this approach was two-fold. Firstly, it enabled us to estimate the weight function of comorbidity severity on ninety-day mortality according to time before cancer diagnosis. Secondly, we could estimate the influence of fixed-effect covariates, such as deprivation group, on the hazard of ninety-day mortality, after adjusting for the time-varying weight function of comorbidity severity.

We ran three alternative WCE models, incorporating either 1, 2 or 3 interior knots for the spline used to estimate the weight function. The best fitting model of the three was selected on the basis of the lowest Bayesian Information Criterion (BIC), using the BIC for censored survival models.[36] Weight functions were right-constrained, i.e. constrained to go to zero on the right, which is applicable to exposures remote in time, such as our six-year lookback for information on the measures of comorbidity.

In the first instance, for each comorbidity-sex sub-group of patients, simple Cox proportional hazards models were used to estimate the hazard ratio of ninety-day mortality adjusting for deprivation group and the non-linear effect of age ("Model 0").

The next step was to estimate the weight function of the time-varying measures of comorbidity on ninety-day mortality, using weighted cumulative exposure (WCE) models.

Our first WCE model included the covariates of deprivation and the non-linear effect of age ("Model 1"), as in Model 0. Subsequent WCE models were then run adding a binary variable indicating whether or not the patient had been diagnosed with colon cancer via emergency presentation ("Model 2"), then a categorical variable indicating multiple comorbidity – i.e. whether the patient had 0,1 or 2+

other comorbidities ("Model 3"). Interactions between age and emergency presentation, age and the multiple comorbidity variable, and deprivation and the multiple comorbidity variable, were tested and removed one by one using a backwards elimination approach, based on that which showed the weakest evidence of significance (based on $p<0.05$) in the model according to the Wald test. The only interaction term that was retained in the WCE model was that between age and emergency presentation for the analysis of male colon cancer patients with diabetes.

Management of the data and the statistical analyses were conducted using Stata 16 statistical software[37] and R software version 3.6.3.[38] The weighted cumulative exposure modelling was undertaken using the "WCE" R package created by Sylvestre and Abrahamowicz.[35]

Results

Patient characteristics

Between 2009 and 2013, 54,425 male patients and 47,791 female patients were diagnosed with colon cancer in England (Table 1). Diabetes and the cardio-vascular conditions were more prevalent among male patients than female patients (13% of males versus 10% of females had diabetes, and 17% males compared with 12% of females had at least one of the cardiovascular conditions). The prevalence of COPD was slightly higher among female patients (14.7% versus 13.9% of male patients).

Among all patients diagnosed with colon cancer, the prevalence (%) of diabetes and the cardiovascular conditions was low (<3.5%) among the younger age groups and rose with increasing age, while the prevalence of COPD according to age group did not follow this pattern. For example, 12% of female patients aged 15-29 and 11.4% of female patients aged 30-44 had COPD compared with 10% of female patients aged 45-59.

The prevalence of each of the three conditions followed a socioeconomic gradient and rose with increasing level of deprivation. For both male and female patients, the biggest difference in prevalence between the least deprived and most deprived groups was widest among patients with COPD.

Diabetes and cardio-vascular conditions were more prevalent among male patients diagnosed with colon cancer via emergency presentation than among female patients with an emergency presentation. Additionally, diabetes, COPD and cardio-vascular conditions were more prevalent among male patients who died within ninety days of colon cancer diagnosis than among females.

Distribution of proxy measures of comorbidity severity according to deprivation group

Number of bed days in hospital

Depending on the deprivation group, approximately 37%-48% of patients with diabetes, 36%-48% of patients with COPD and 23%-30% patients with one or more of the cardiovascular conditions spent 7 or less bed days in hospital in the six years prior to cancer diagnosis (Figure 2, Appendix Table 2). Among the most deprived groups of patients with the comorbidities of interest, 27% of the patients with COPD or with diabetes and 38% of the patients with one of more of the cardio-vascular conditions had been in hospital for at least 31 bed days during the six year period, versus 17%, 10% and 29% of the least deprived patients with diabetes, COPD or the cardio-vascular conditions, respectively.

Time with comorbidity

Diabetes, COPD or cardio-vascular conditions were first recorded in hospital admissions occurring up to one year prior to cancer diagnosis for approximately 40-50% of patients with these conditions in each deprivation group. A higher percentage of patients in the most deprived group had been living with their respective condition for 5-6 years compared with the least deprived group, for example,

13% of the most deprived group versus 10% of the least deprived group with COPD had the condition for 5-6 years (Appendix Figure 2).

Frequency of hospital admissions

The majority of patients in each of the deprivation groups had hospital admissions occurring from 1 to 3 of the months in the six-year period before cancer diagnosis: approximately 70% of patients with diabetes, 83% - 88% of patients with COPD and approximately 67% of patients with one or more of the cardio-vascular conditions (Appendix Figure 3).

Weighted cumulative exposure models

In comparing the weighted cumulative exposure models according to whether the weight function was derived from splines with 1, 2 or 3 internal knots, the models considered to be the best fitting – i.e. based on the lowest BIC - were those with 1 internal knot (Appendix Table 3).

Weight function of each comorbidity on ninety-day mortality

The weight function of the exposure measures of diabetes differed between male and female patients in terms of magnitude and shape (Appendix Figure 4). The weight function of diabetes on ninety-day mortality for male patients fluctuated according to the length of time the condition was present before cancer diagnosis. Following adjustment for emergency presentation (models 2 and 3) the weight function followed a stable decrease over time for female patients.

The weight function of COPD for female patients was negative up until approximately 3 years prior to cancer diagnosis, suggesting that during this timeframe these measures of COPD exposure could offer a protective effect toward the risk of ninety-day colon cancer mortality (Appendix Figure 5). By

contrast the weight function of COPD exposure of male patients appeared to suggest exposure had a protective effect on the risk of ninety-day mortality up to 3 years before cancer diagnosis.

For female patients, the weight function of the exposure of cardio-vascular conditions up to approximately 4.5 years prior to cancer diagnosis (following adjustment for emergency presentation) was negative, thus suggesting that the exposure had a protective effect on the risk of ninety-day mortality (Appendix Figure 6). However, for male patients, the weight function of cardio-vascular conditions was positive. Given that the confidence intervals of the weight functions estimated for male and female patients with COPD and female patients with cardio-vascular conditions span across zero, the negative values of the weight function should be interpreted with some caution.

Socioeconomic deprivation and ninety-day mortality

Our study aimed to investigate socioeconomic inequalities in ninety-day mortality before and after estimating, and adjusting for, the weight function of each comorbidity. The hazard ratio of the most deprived group of patients compared with the least deprived group of patients, of each comorbidity-sex patient sub-group and for each of the four models run are summarised in Figure 3. Within each sub-group of patients, based on the Cox regression model adjusting for age and deprivation (Model 0), the most deprived patients had a higher hazard of mortality than the least deprived groups, ranging from a 25% increased hazard among the most deprived male patients with COPD (HR 1.25; 95%CIs: 1.05, 1.48) to a 71% increased hazard among the most deprived female patients with COPD (HR 1.71; 1.42, 2.07). After adjusting for the time-varying effects of each respective comorbidity in the WCE framework (Model 1) the hazard ratio reduced (from that derived from Model 0), this was the case regardless of the comorbidity or the sex of the patient. The excess hazard of mortality of the most deprived versus least deprived male patients with COPD went from 25% to weak evidence of an 8% increased hazard of ninety-day mortality (HR 1.08; 0.91, 1.28, Model 1). By contrast, among female

patients with COPD, the most deprived patients still had a 60% increased hazard of mortality compared with the least deprived group (HR 1.60; 1.32, 1.92, Model 1).

There were also differences between the sexes in respect to socioeconomic inequalities in mortality among patients with diabetes or cardiovascular conditions. The increased mortality hazard of the most versus least deprived patients with diabetes was 31% among male patients while only 18% among female patients with diabetes (HR 1.31, 1.08, 1.58 and HR 1.18, 0.95, 1.47, respectively). Among patients with cardio-vascular conditions, the most deprived female patients had a 37% increased mortality hazard while the most deprived male patients had a 25% increased hazard of mortality versus the least deprived patients (HR 1.37; 1.16, 1.61, and HR 1.25; 1.09, 1.44, respectively).

Further adjustment for emergency presentation (Model 2), and then for the presence of multiple other comorbidities (Model 3) brought further reductions to the hazard ratio of the most deprived versus least deprived groups of patients in each patient sub-group. The remaining difference in mortality between the most and least deprived groups of patients ranged from no evidence of a difference among male patients with COPD (HR 1.00; 0.85, 1.19) to a 40% increased hazard among the most deprived female patients with COPD (HR 1.40; 1.16, 1.69).

To further examine the relationship between deprivation and ninety-day mortality among patients with diabetes, COPD or cardio-vascular conditions, the mortality hazard between the time of cancer diagnosis and 90 days after, according to deprivation group (most and least deprived groups), age at cancer diagnosis, emergency cancer diagnosis and the presence of multiple other comorbidities was derived from Model 3. These results are represented as the hazard ratio of ninety-day mortality at different combinations of these prognostic factors, referenced to the least deprived group aged 70 years at cancer diagnosis without emergency presentation and without other comorbidities, and presented by comorbidity and sex in Figures 4-6.

Ninety-day mortality among patients with diabetes

The deprivation gap in ninety-day mortality – i.e. the additional risk of mortality of the most deprived versus least deprived groups of patients - was wider among the male patients with diabetes than among the female patients with diabetes, and evidence of inequalities was weaker among female patients (Figures 3 and 4). Being diagnosed with cancer via emergency presentation had more of an impact on mortality among male patients than female patients. For example, among 50 year old male patients with diabetes and diagnosed with cancer as an emergency, the most deprived patients had approximately 3.4 times the hazard of ninety-day mortality (HR 3.38; 95%CIs: 1.11, 10.28) compared with the reference group (least deprived patients aged 70 at cancer diagnosis without emergency presentation and without other comorbidities), while the most deprived 50 year old female patients had 2.3 times the mortality hazard of their respective reference group (HR 2.31; 2.29, 2.33). The most deprived 70-year-old male patients who had multiple other comorbidities and had been diagnosed with colon cancer via emergency presentation had 7.5 times the hazard of ninety-day mortality of the reference group of 70-year-old patients (HR 7.52; 4.19, 13.49). Among the most deprived 70-year-old female patients, the mortality hazard was 6.8 times that of the reference group (HR 6.81; 3.96, 11.72).

Ninety-day mortality among patients with COPD

The contrast between male and female colon cancer patients with COPD, in respect to the influence that deprivation or having multiple additional comorbidities had on the hazard of ninety-day mortality is demonstrated in Figure 5. Among male patients there was no evidence of a difference in the hazard of mortality between the most and least deprived groups, while among female patients there was an obvious deprivation gap, regardless of the status of the other prognostic factors.

As an example of the increased hazard of mortality from having multiple other comorbidities, the most deprived female patients aged 70 years at cancer diagnosis with additional comorbidities had 2.4 times the mortality hazard within ninety days of diagnosis (HR 2.35; 1.46, 3.27) of their respective reference group (reference group as described previously). However, male patients aged 70 with multiple other comorbidities had approximately 1.25 times the mortality hazard of their reference group (HR 1.27; 1.11, 1.73).

The hazard of ninety-day mortality following emergency presentation with colon cancer was broadly similar among male or female patients but followed a steeper gradient with age among male patients. However, where patients also had multiple other comorbidities the differences between the sexes in hazard of mortality was quite striking. For example, the most deprived such female patients aged 70 had approximately 9 times the mortality hazard (HR: 8.97; 5.64, 14.24), while the most deprived such male patients aged 70 had approximately 4.6 times the mortality hazard (HR 4.62; 3.01, 7.10) of their respective reference groups.

Ninety-day mortality among patients with cardio-vascular conditions

In comparing the two sexes, socioeconomic inequalities in ninety-day mortality were most pronounced among the female colon cancer patients with cardio-vascular conditions (Figure 6). An emergency diagnosis of colon cancer had a similar impact on mortality among male and female patients: the least deprived patients diagnosed with colon cancer via emergency presentation at age 70 had approximately 4 times the hazard of ninety-day mortality compared with their respective reference group (HR: 3.89; 3.52, 4.31 and HR: 3.97; 3.52, 4.48 for males and females, respectively). The presence of two or more additional comorbidities had a bigger influence on ninety-day mortality among female patients than male patients. Among patients who had an emergency cancer diagnosis and were living with multiple additional comorbidities, the most deprived 70-year-old female patients had 6.6 times the hazard of mortality of the reference group (HR: 6.65; 4.40, 10.04), while among the

most deprived 70 year old male patients the hazard was 5 times that of their respective reference group (HR: 4.95; 3.48, 7.06).

Discussion

The findings of our study indicated that accounting for the weight function of time with comorbidity and timing and duration of hospital admissions while living with comorbidity reduced socioeconomic inequalities in all-cause ninety-day mortality. Depending on the comorbidity-sex sub-group studied, the reduction in the inequalities in mortality ranged from 12% to 68%. After adjusting for these time-varying measures of comorbidity and other prognostic factors, socioeconomic inequalities in mortality persisted among all but one of the sub-groups of patients (the male patients with COPD). The magnitude of the inequalities varied according to the respective comorbidity, sex of the patient, and the values of other prognostic factors. Among the male patients with COPD there was no evidence to suggest a difference in mortality between the most and least deprived groups of patients after adjustment for the prognostic factors. By contrast, between the remaining patient groups, the widest socioeconomic inequalities were seen among female patients with COPD: as an example to quantify these inequalities, the most deprived patients aged 70 years at cancer diagnosis had a 40% increased hazard of ninety-day mortality compared with the least deprived group.

The reduction in socioeconomic inequalities in ninety-day mortality that followed the adjustment for timing of comorbidity and hospital admissions, suggests healthcare utilisation may explain part of these inequalities. Differences in healthcare utilisation between the most and least deprived groups of patients could warrant further consideration. Within the sub-groups of patients we studied, a higher percentage of patients in the most deprived group had been living with their condition at least

five to six years, had been in hospital for ninety or more bed days or had been admitted to hospital during at least ten of the months while living with the comorbidity prior to cancer diagnosis, regardless of the comorbidity, as compared with the least deprived group (Appendix Table 2). Moreover, a study of the impact of deprivation on patient health care costs in England showed that the health care costs of the most deprived patients were higher than that of the less deprived groups, which is reflective of more frequent usage and / or an increased burden of disease among the most deprived group.[39] Emergency presentation was a strong prognostic factor of increased ninety-day mortality in this study, irrespective of sex or comorbidity, which concurs with other research findings regarding the influence of emergency presentation on short-term mortality among patients with colorectal cancer.[34] Adjusting for emergency presentation in our WCE models further reduced the socioeconomic inequalities in mortality within each of the patient sub-groups, indicating that the most deprived patients were more adversely impacted following an emergency diagnosis. While stage at diagnosis is a prognostic factor in short-term cancer mortality,[40] we considered that time with comorbidity may influence the stage at which cancer is diagnosed[41] and therefore stage at diagnosis is on the causal pathway in the relationship between time with comorbidity and ninety-day mortality (Appendix Figure 1). For this reason, we did not consider stage as a potential confounder and did not adjust for it in our analyses.

The outcomes of comorbid cancer patients may not only be influenced by the various prognostic factors of the cancer, but also the severity of their comorbidity, and the influence the comorbidity has on the management of the cancer. Indeed, the most deprived cancer patients with comorbidity may be faced with disadvantage over the least deprived patients with comorbidity even before cancer diagnosis, as lower socioeconomic position is associated with poorer outcomes with various chronic health conditions, including diabetes,[42, 43] COPD[44] and cardio-vascular conditions.[45]

On this basis, our findings in respect to the diminished socioeconomic inequalities in mortality among male patients with COPD were unexpected, particularly given their contrast with the findings for

female patients with COPD. There is evidence to support differences between the sexes in terms of clinical expression and outcomes of COPD: female patients with COPD may have worse symptoms,[46, 47] worse health-related quality of life[47, 48] and higher all-cause or respiratory mortality[49] than males. While this could be an explanation for poorer all-cause mortality among the female versus male colon cancer patients with COPD in our study, it does not explain the sex differences in respect to socioeconomic deprivation and mortality. Women may be more vulnerable to the toxic effects of tobacco than men[50, 51] while tobacco smoking - a known risk factor for COPD[52, 53] - is generally more prevalent among more deprived groups.[54] It would have been useful to have information on smoking status in our data, to see if prevalence of smoking differed substantially between male and female patients and between deprivation groups of the patients with COPD, and to investigate whether this was connected with the socioeconomic inequalities in mortality among the female colon cancer patients with COPD.

In our study, socioeconomic inequalities in all-cause mortality persisted among patients with one of the cardio-vascular conditions; these inequalities appeared to be wider within female patients than male patients. The results of a study by Stringhini and colleagues showed that behavioural factors (smoking, physical activity levels), and physiological factors (inflammatory markers) could partly explain an association between low socioeconomic position and cardiovascular disease mortality in England,[55] but whether this association differed according to sex was not discussed.

Among patients with diabetes, there was weaker evidence that socioeconomic inequalities in ninety-day mortality remained once the time-varying measures of comorbidity and other prognostic factors had been accounted for, particularly among the female patients. As the healthcare system in the UK places focus on managing diabetes within primary care,[56] we made the assumption that patients requiring hospital care for diabetes represent those patients with complicated diabetes or diabetes that cannot be well managed within primary care.[57] It is also possible that those presenting to hospital

via emergency admission with complications of diabetes, tend to be of a lower socioeconomic position. [42, 43]

Searching the scientific literature returned few studies investigating similar measures of comorbidity, suggesting these measures (and the influence they have on short-term mortality) may not have been well-studied. Shack and colleagues investigated different time windows of comorbidity in relation to one-year survival from colorectal cancer, among a population-based cohort of patients in the North West of England. They concluded that comorbid conditions recorded up to 18 months before the cancer diagnosis were more strongly associated with an excess hazard of death within one-year of cancer diagnosis than comorbidities recorded up to one year after cancer diagnosis or at any time.[24] However, the timing of comorbidity did not appear to influence the impact it had on all-cause mortality among older, early-stage breast cancer patients.[58] We found one other study within the scientific literature that had used a similar approach to ours for defining or measuring comorbidity. This was an Australian study that modelled comorbidity presence, recency, duration and severity (not specific to any one primary disease) in respect to the risk of post-hospitalisation mortality and readmission, using administrative data. The Australian study concluded that models with four measures of comorbidity (presence, recency, duration and severity) offered a better model-fit than those modelling the presence of comorbidity only.[59] While that study used Cox regression models to investigate post-hospitalisation outcomes based upon these measures of comorbidity, we estimated the weight function of presence of and timing and duration of hospital admissions with comorbidity on ninety-day mortality using Weighted Cumulative Exposure (WCE) models. Although this is a novel approach to investigating cancer comorbidity, it is an established method in the pharmaco-epidemiology setting and is used to investigate the impact of recency, timing and dose of drugs on patient outcomes.[35, 60] The design of our study was such that the event of interest (ninety-day mortality) could only occur after cancer diagnosis and not during the period in which our time-varying

measures of comorbidity occurred. However, using WCE models provided us with the opportunity to adjust for the weighted time-varying effect of time with comorbidity, frequency and duration of hospital admissions prior to cancer diagnosis when estimating socioeconomic inequalities in ninety-day mortality among comorbid colon cancer patients.

In this study we were faced with certain limitations that related to our data. To obtain information on comorbidity, we were reliant on the patient requiring hospital care and the comorbidities being well-recorded in the diagnostic fields of the hospital admissions data. Additionally, there was no means of verifying the primary reason for hospital admission. We acknowledge the possibility of measurement error or misclassification within these data. However, we assume that while some less severe conditions, such as obesity, or conditions such as diabetes may be underreported in these data, that the more severe conditions are likely to require hospital care and will be captured within the diagnostic fields of these data.

Nonetheless, the findings of this study provide insight into factors influencing socioeconomic inequalities in ninety-day mortality among colon cancer patient with diabetes, COPD or cardio-vascular comorbidities. Time with comorbidity and timing and duration of hospital admissions appeared to explain some of these inequalities, as did having an emergency diagnosis of colon cancer. Further investigation of differences in patterns in healthcare utilisation according to deprivation group could be informative in further disentangling the mechanisms behind inequalities in short-term cancer outcomes among cancer patients with comorbidity. For example, identifying opportunities for earlier cancer diagnosis among the most deprived patients with pre-existing comorbidities, particularly those comorbidities considered as risk factors for developing cancer.

Further future research to confirm the unexpected findings of this study and to understand the mechanisms leading to these findings would be beneficial.

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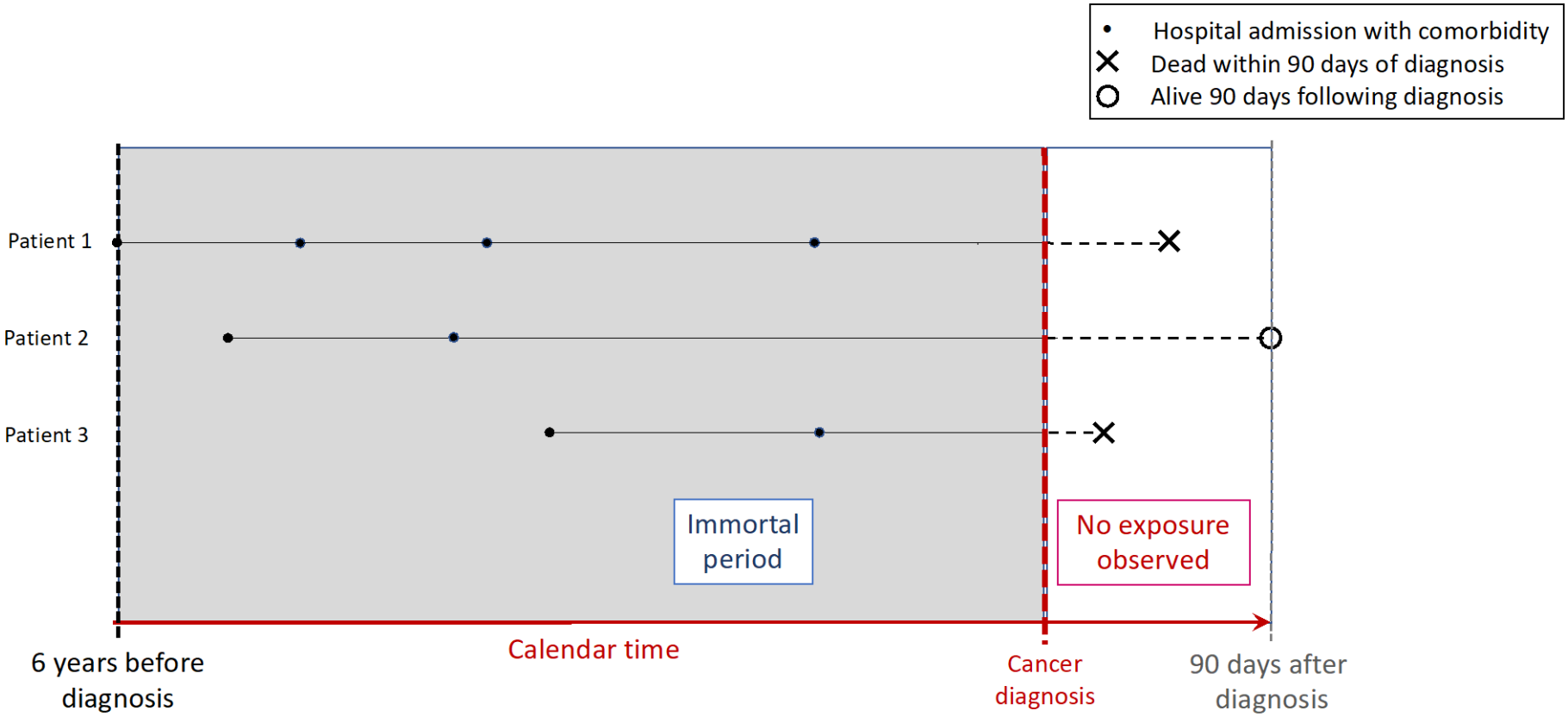
Figure 1: Illustration of the exposure and event time of the study, with three hypothetical patient scenarios



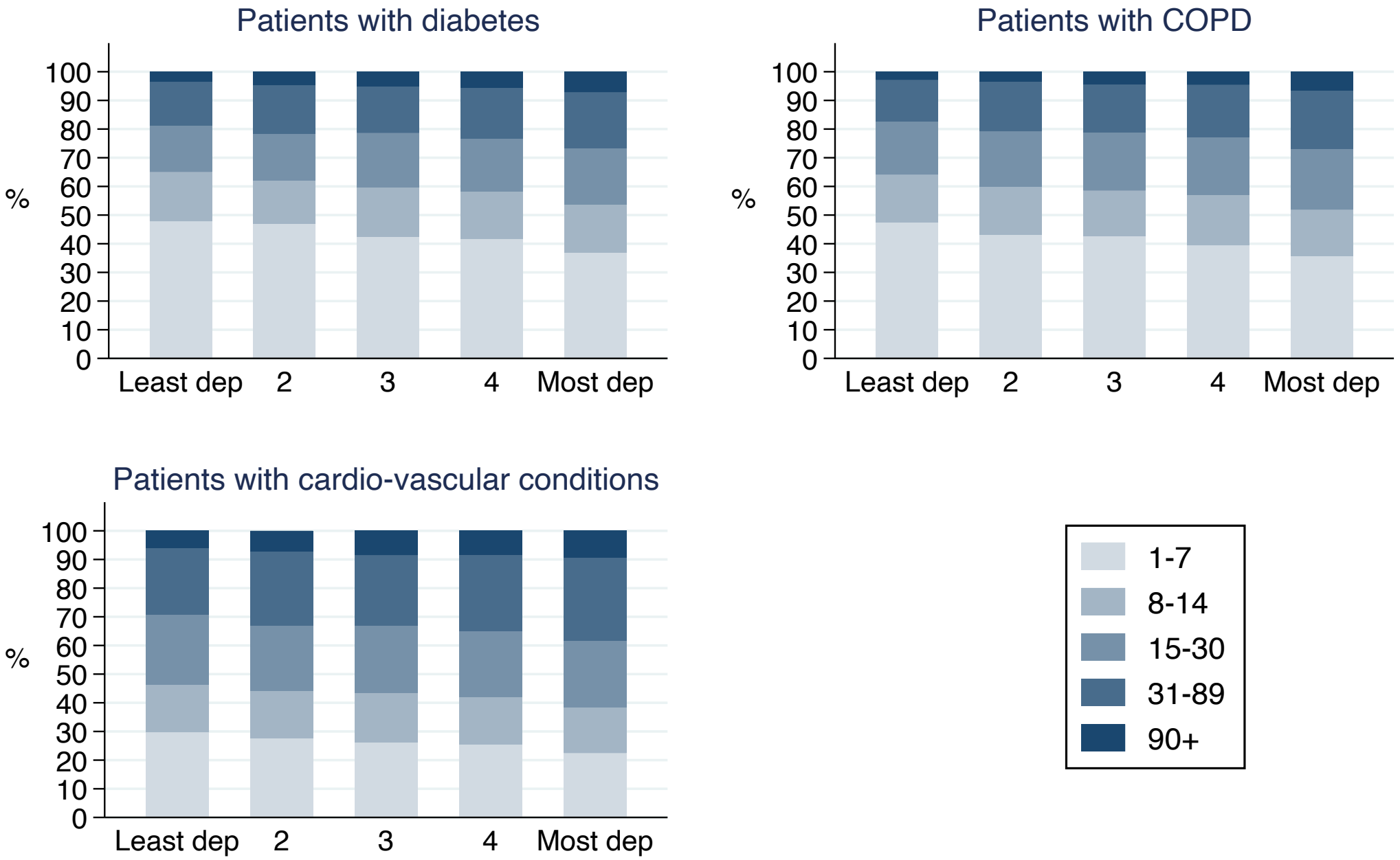
Patient scenarios

Patient 1: Has hospital admission with comorbidity at the start of the six-year comorbidity lookback period, has three further hospital admissions before cancer diagnosis, and dies within ninety days of cancer diagnosis

Patient 2: Has two hospital admissions with comorbidity in the six-year period before cancer diagnosis and is alive at ninety days following cancer diagnosis

Patient 3: Has two hospital admissions with comorbidity in the six-year period before cancer diagnosis and dies within ninety days of cancer diagnosis

Figure 2: Number of bed days in hospital with comorbidity in the six years before cancer diagnosis, according to deprivation group

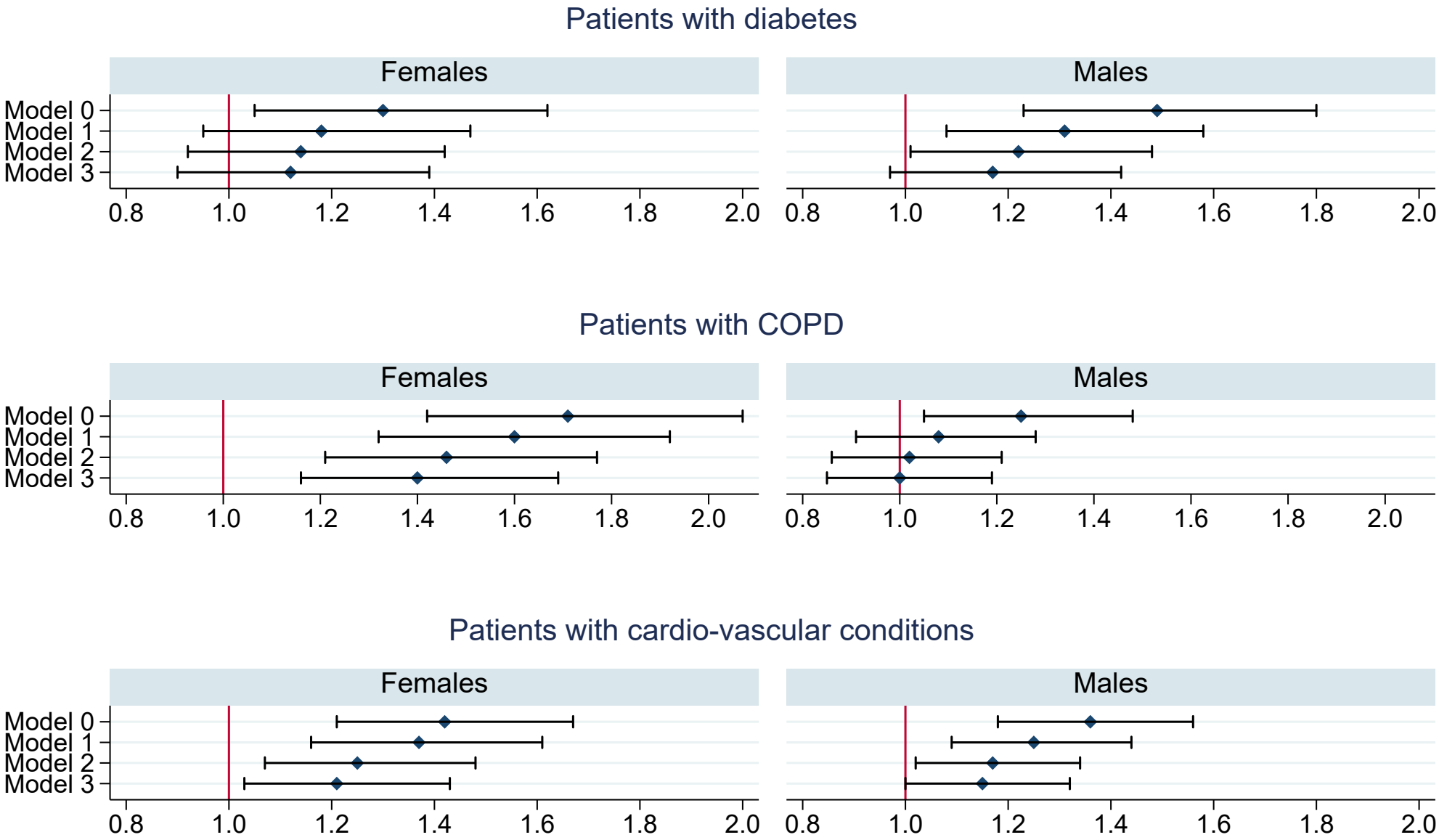


COPD: Chronic obstructive pulmonary disease; dep: deprived

Table 1: Presence of the comorbid conditions of interest among patients diagnosed with colon cancer between 2009 and 2013 in England, by patient characteristics

	Males								Females							
	All patients		With diabetes		With COPD		With cardio-vascular conditions		All patients		With diabetes		With COPD		With cardio-vascular conditions	
Patient characteristics	N	*% male patients*	n	*% male patients with diabetes*	n	*% male patients with COPD*	n	*% male patients with cardio-vascular conditions*	N	*% female patients*	n	*% female patients with diabetes*	n	*% female patients with COPD*	n	*% female patients with cardio-vascular conditions*
Age (years)																
15-29	326	*0.6*	0	*0.0*	34	*0.4*	0	*0.0*	443	*0.9*	1	*<0.1*	53	*0.8*	1	*<0.1*
30-44	1,299	*2.4*	29	*0.4*	95	*1.3*	16	*0.2*	1,367	*2.9*	46	*1.0*	156	*2.2*	10	*0.2*
45-59	6,328	*11.6*	473	*6.8*	514	*6.8*	323	*3.5*	5,643	*11.8*	277	*6.0*	557	*7.9*	136	*2.4*
60-74	24,150	*44.4*	3,041	*43.5*	2,955	*39.0*	3,107	*33.7*	18,016	*37.7*	1,624	*35.1*	2,527	*36.0*	1,252	*22.4*
75-90	22,322	*41.0*	3,451	*49.3*	3,980	*52.5*	5,772	*62.6*	22,322	*46.7*	2,676	*57.9*	3,730	*53.1*	4,201	*75.0*
Deprivation (IMD income)																
Least deprived	12,149	*22.3*	1,305	*18.7*	1,308	*17.3*	1,798	*19.5*	10,262	*21.5*	758	*16.4*	1,201	*17.1*	993	*17.7*
2	12,136	*22.3*	1,458	*20.8*	1,485	*19.6*	1,902	*20.6*	10,487	*21.9*	848	*18.3*	1,319	*18.8*	1,135	*20.3*
3	11,296	*20.8*	1,442	*20.6*	1,484	*19.6*	1,908	*20.7*	10,295	*21.5*	976	*21.1*	1,452	*20.7*	1,171	*20.9*
4	10,483	*19.3*	1,480	*21.2*	1,667	*22.0*	1,915	*20.8*	9,457	*19.8*	1,078	*23.3*	1,600	*22.8*	1,257	*22.4*
Most deprived	8,361	*15.4*	1,309	*18.7*	1,634	*21.6*	1,695	*18.4*	7,290	*15.3*	964	*20.8*	1,451	*20.7*	1,044	*18.6*
Emergency presentation																
Yes	14,191	*26.1*	2,084	*29.8*	2,581	*34.1*	3,443	*37.4*	13,937	*29.2*	1,593	*34.5*	2,535	*36.1*	2,611	*46.6*
No	40,234	*73.9*	4,910	*70.2*	4,997	*65.9*	5,775	*62.6*	33,854	*70.8*	3,031	*65.5*	4,488	*63.9*	2,989	*53.4*
Death within ninety days of colon cancer diagnosis																
Yes	7,608	*14.0*	1,174	*16.8*	1,450	*19.1*	2,140	*23.2*	7,105	*14.9*	913	*19.7*	1,324	*18.9*	1,686	*30.1*
No	46,817	*86.0*	5,820	*83.2*	6,128	*80.9*	7,078	*76.8*	40,686	*85.1*	3,711	*80.3*	5,699	*81.1*	3,914	*69.9*
Stage at diagnosis																
1	4,663	*8.6*	612	*8.8*	687	*9.1*	721	*7.8*	3,618	*7.6*	317	*6.9*	552	*7.9*	325	*5.8*
2	9,910	*18.2*	1,344	*19.2*	1,361	*18.0*	1,652	*17.9*	9,066	*19.0*	865	*18.7*	1,380	*19.6*	962	*17.2*
3	9,289	*17.1*	1,177	*16.8*	1,207	*15.9*	1,430	*15.5*	8,207	*17.2*	835	*18.1*	1,126	*16.0*	860	*15.4*
4	11,972	*22.0*	1,541	*22.0*	1,599	*21.1*	1,862	*20.2*	10,244	*21.4*	978	*21.2*	1,455	*20.7*	1,094	*19.5*
Missing	18,591	*34.2*	2,320	*33.2*	2,724	*35.9*	3,553	*38.5*	16,656	*34.9*	1,629	*35.2*	2,510	*35.7*	2,359	*42.1*
TOTAL	**54,425**	***100.00***	**6,994**	*12.9*	**7,578**	*13.9*	**9,218**	*16.9*	**47,791**	*100.00*	**4,624**	*9.7*	**7,023**	*14.7*	**5,600**	*11.7*

Figure 3: Adjusted hazard ratios (HR) of ninety-day mortality:
Most deprived versus least deprived colon cancer patients, according to model

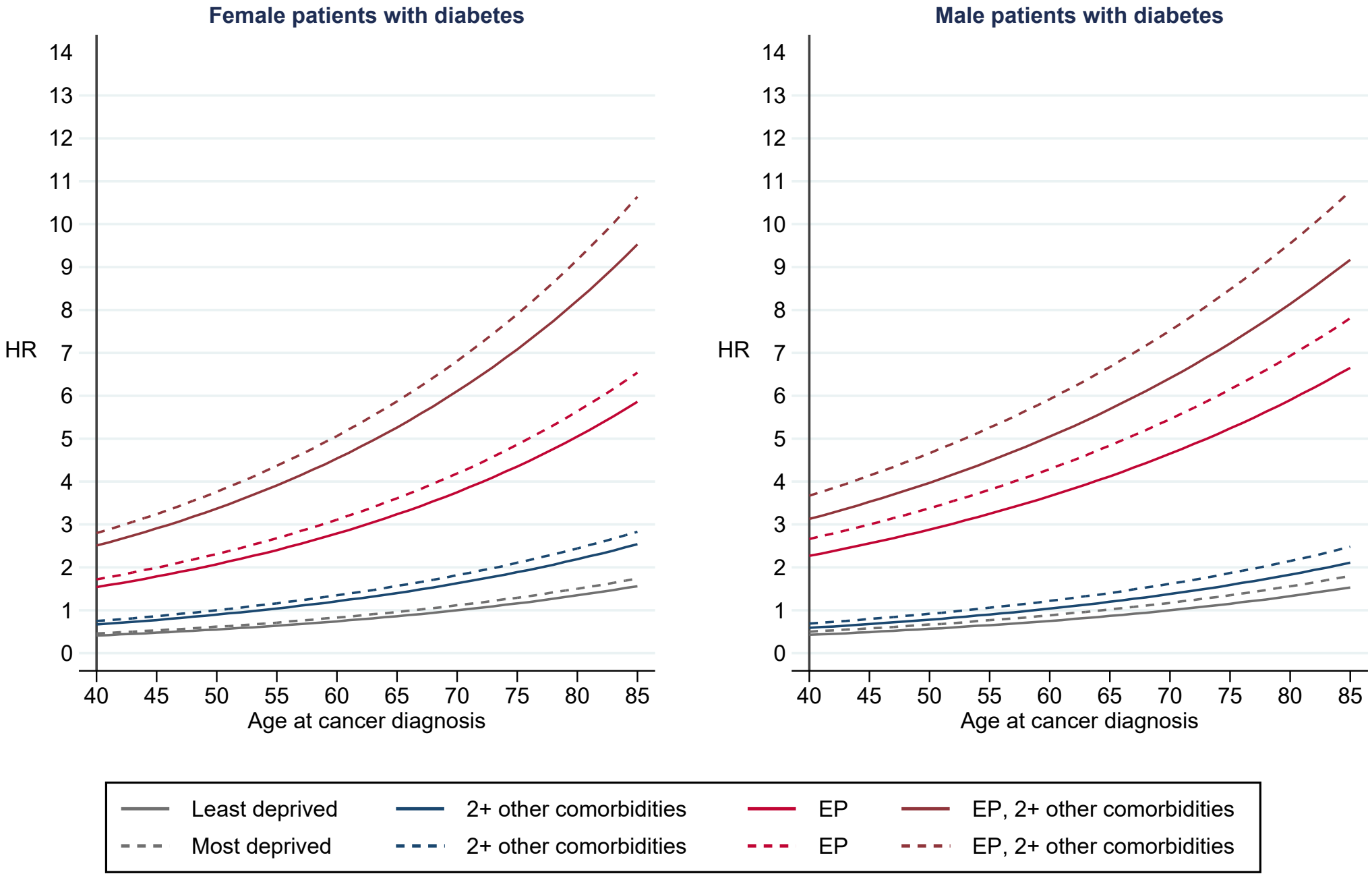


HR of patients aged 70 at cancer diagnosis (least deprived = 1)

Model 0: age and deprivation; **Model 1**: (WCE) age and deprivation; **Model 2**: Model 1 + EP; **Model 3**: Model 2 + other comorbidities
Abbreviations - COPD: Chronic obstructive pulmonary disease; WCE: weighted cumulative exposure; EP: emergency presentation

Figure 4: Hazard ratio of ninety-day mortality by age at cancer diagnosis

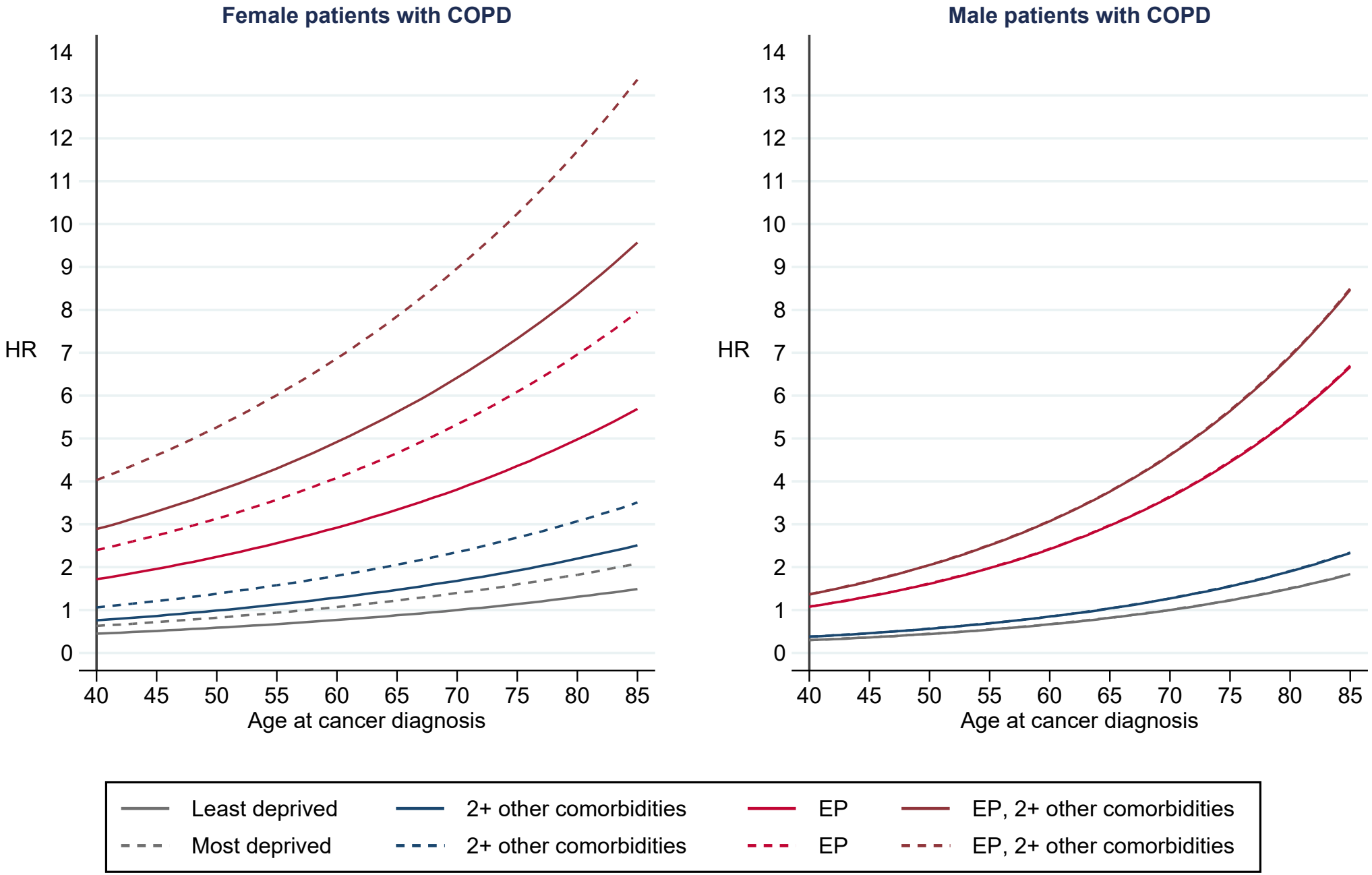
According to least or most deprived group, emergency presentation (EP), and presence of 2 or more other comorbidities



Note: Hazard ratio reference is the least deprived group of patients at age 70 without emergency presentation and without other comorbidities

Figure 5: Hazard ratio of ninety-day mortality by age at cancer diagnosis

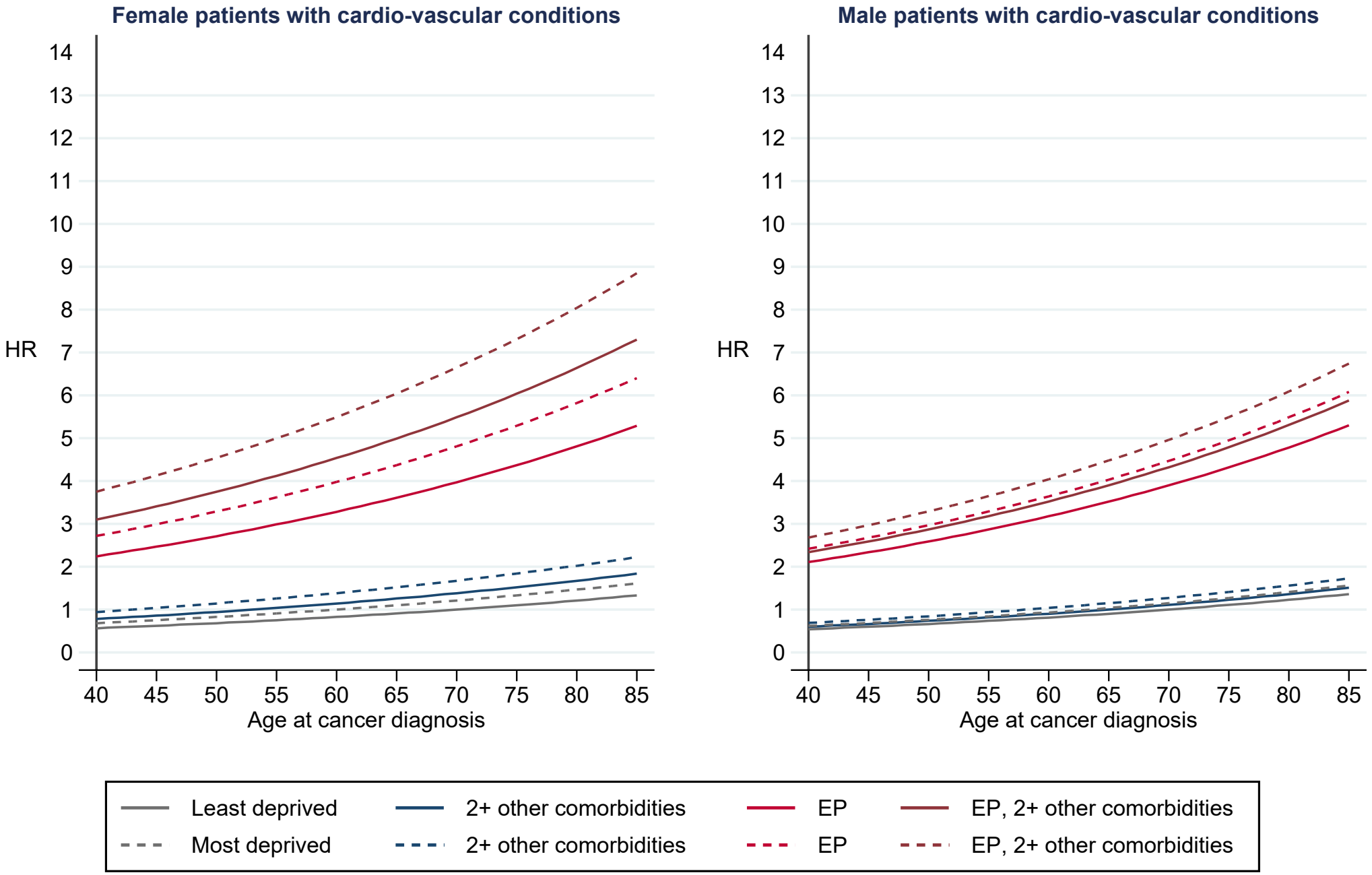
According to least or most deprived group, emergency presentation (EP), and presence of 2 or more other comorbidities



Note: Hazard ratio reference is the least deprived group of patients at age 70 without emergency presentation and without other comorbidities

Figure 6: Hazard ratio of ninety-day mortality by age at cancer diagnosis

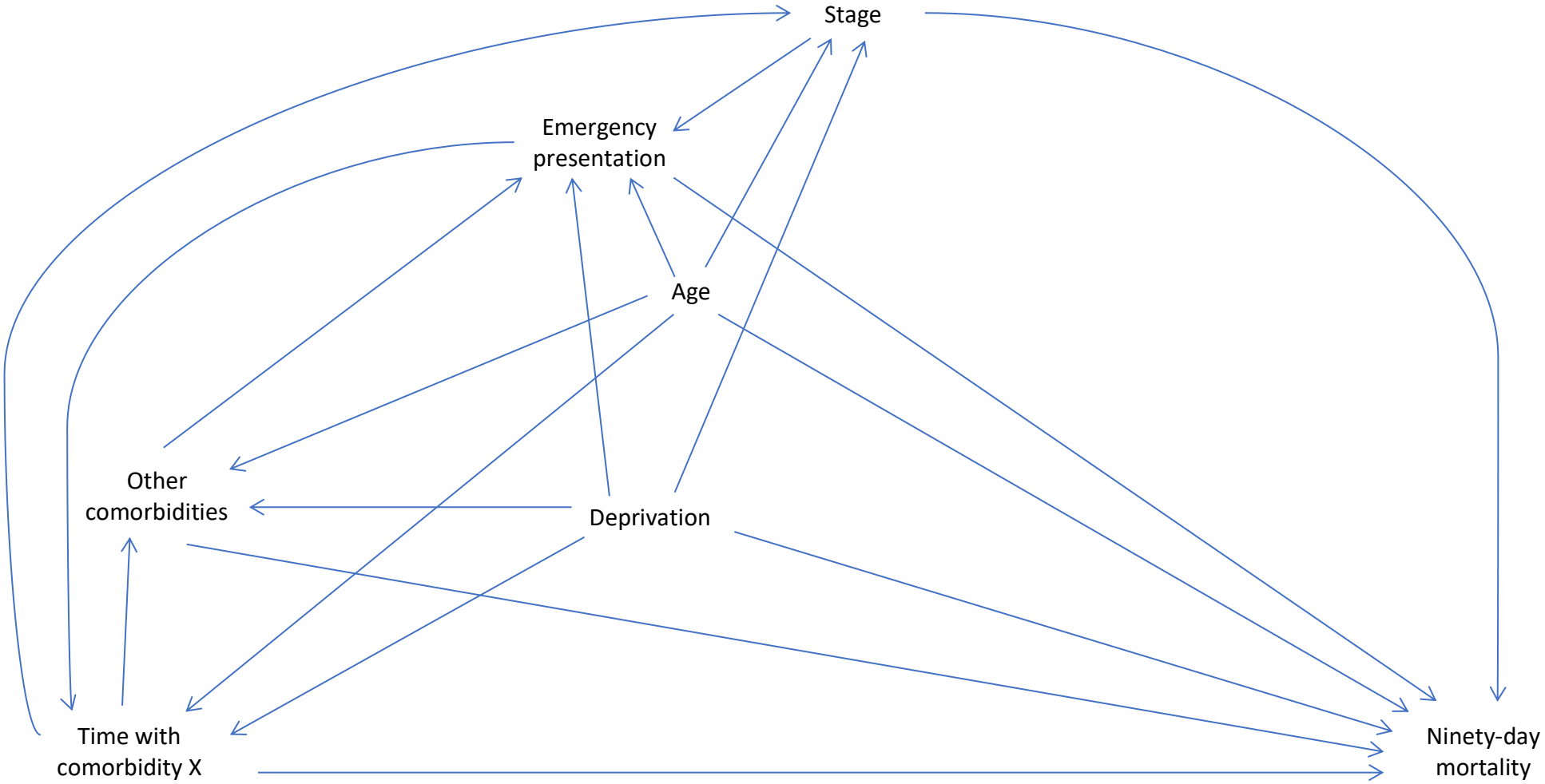
According to least or most deprived group, emergency presentation (EP), and presence of 2 or more other comorbidities



Note: Hazard ratio reference is the least deprived group of patients at age 70 without emergency presentation and without other comorbidities

Appendix Table 1: Data format example

Patient id	Interval start (month number)	Interval end (month number)	Exposure (number of bed days)	Outcome (ninety-day mortality)
1	0	1	4	0
1	1	2	0	0
1	2	3	0	0
1	…	…	0	0
1	15	16	3	0
1	…	…	0	0
1	26	27	8	0
1	…	…	0	0
1	54	55	15	0
1	…	…	0	0
1	72	73	0	0
1	73	74	0	1
2	0	1	0	0
2	…	…	0	0
2	12	13	5	0
2	…	…	0	0
2	23	24	2	0
2	…	…	0	0
2	72	73	0	0
2	73	74	0	0
2	74	75	0	0
3	0	1	0	0
3	…	…	0	0
3	33	34	10	0
3	…	…	0	0
3	56	57	20	0
3	…	…	0	0
3	72	73	0	1

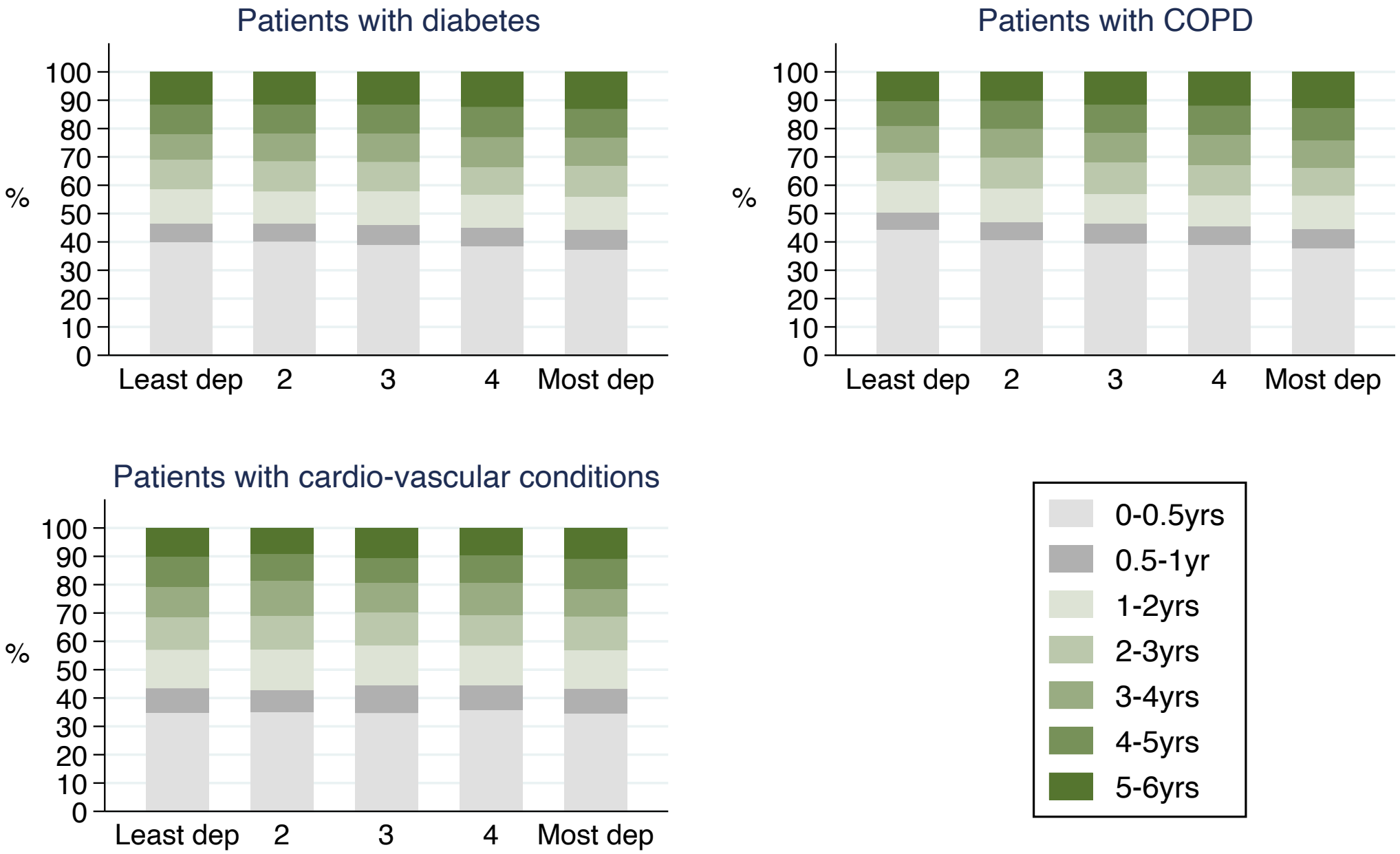


Appendix Figure 1: Directed acyclic graph (DAG) depicting the assumed causal relationships between deprivation and other prognostic factors, time with a comorbidity and ninety-day mortality.

Appendix Table 2: Distribution of time living with comorbidity and frequency and duration of hospital admissions, by patient deprivation group

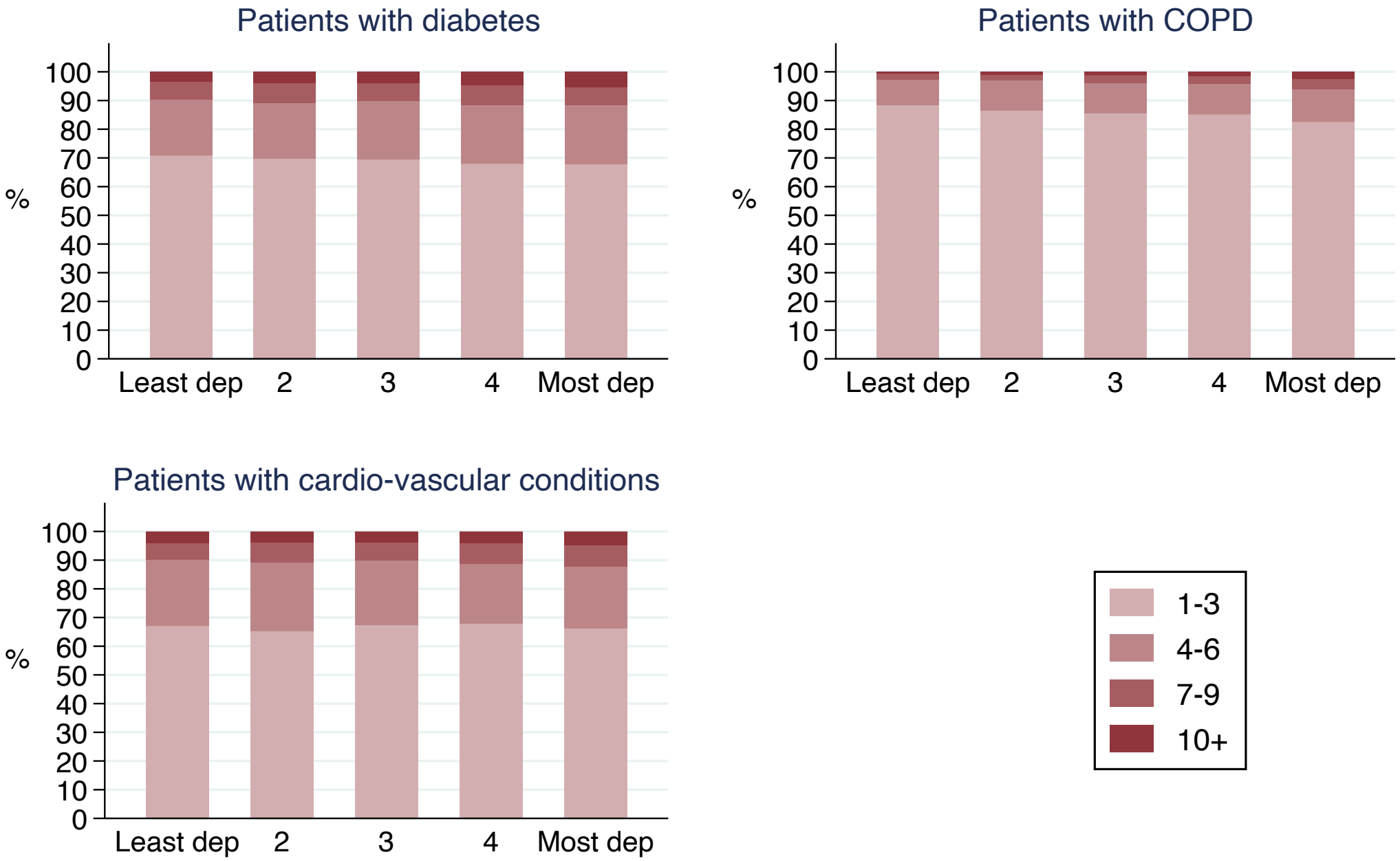
	Deprivation group									
	Least deprived (1)		2		3		4		Most deprived (5)	
	n	%	n	%	n	%	n	%	n	%
Time before cancer diagnosis when comorbidity first recorded										
Diabetes										
0-0.5 years	826	40.0	925	40.1	942	39.0	986	38.5	850	37.4
0.5-1 year	133	6.4	150	6.5	172	7.1	168	6.6	157	6.9
1-2 years	254	12.3	258	11.2	286	11.8	297	11.6	265	11.7
2-3 years	211	10.2	246	10.7	250	10.3	249	9.7	248	10.9
3-4 years	189	9.2	227	9.8	246	10.2	269	10.5	227	10.0
4-5 years	212	10.3	236	10.2	245	10.1	273	10.7	229	10.1
5-6 years	238	11.5	264	11.4	277	11.5	316	12.4	297	13.1
COPD										
0-0.5 years	1,114	44.4	1,144	40.8	1,158	39.4	1,278	39.1	1,165	37.8
0.5-1 year	153	6.1	173	6.2	208	7.1	208	6.4	211	6.8
1-2 years	276	11.0	333	11.9	304	10.4	358	11.0	362	11.7
2-3 years	252	10.0	308	11.0	330	11.2	348	10.7	305	9.9
3-4 years	235	9.4	283	10.1	306	10.4	353	10.8	296	9.6
4-5 years	222	8.8	277	9.9	291	9.9	333	10.2	354	11.5
5-6 years	257	10.2	286	10.2	339	11.5	389	11.9	392	12.7
Cardio-vascular conditions										
0-0.5 years	970	34.8	1,063	35.0	1,068	34.7	1,137	35.8	948	34.6
0.5-1 year	242	8.7	237	7.8	304	9.9	278	8.8	236	8.6
1-2 years	379	13.6	436	14.4	431	14.0	440	13.9	375	13.7
2-3 years	323	11.6	364	12.0	359	11.7	345	10.9	327	11.9
3-4 years	299	10.7	371	12.2	321	10.4	359	11.3	267	9.7
4-5 years	296	10.6	290	9.5	271	8.8	308	9.7	287	10.5
5-6 years	282	10.1	276	9.1	325	10.6	305	9.6	299	10.9
Number of months with a hospital admission										
Diabetes										
1-3	1,461	70.8	1,607	69.7	1,684	69.6	1,738	67.9	1,541	67.8
4-6	405	19.6	450	19.5	487	20.1	526	20.6	469	20.6
7-9	126	6.1	159	6.9	150	6.2	174	6.8	143	6.3
10+	71	3.4	90	3.9	97	4.0	120	4.7	120	5.3
COPD										
1-3	2,216	88.3	2,426	86.5	2,511	85.5	2,782	85.2	2,546	82.5
4-6	227	9.0	296	10.6	308	10.5	351	10.7	354	11.5
7-9	50	2.0	55	2.0	82	2.8	86	2.6	107	3.5
10+	16	0.6	27	1.0	35	1.2	48	1.5	78	2.5
Cardio-vascular conditions										
1-3	1,871	67.0	1,980	65.2	2,073	67.3	2,154	67.9	1,816	66.3
4-6	646	23.1	727	23.9	693	22.5	658	20.7	587	21.4
7-9	163	5.8	214	7.0	196	6.4	232	7.3	207	7.6
10+	111	4.0	116	3.8	117	3.8	128	4.0	129	4.7
Total number of bed days										
Diabetes										
1-7	987	47.8	1,083	47.0	1,025	42.4	1,065	41.6	840	37.0
8-14	355	17.2	348	15.1	417	17.2	427	16.7	383	16.8
15-30	335	16.2	377	16.3	460	19.0	468	18.3	443	19.5
31-89	314	15.2	390	16.9	394	16.3	456	17.8	445	19.6
90+	72	3.5	108	4.7	122	5.0	142	5.6	162	7.1
COPD										
1-7	1,192	47.5	1,208	43.1	1,254	42.7	1,289	39.5	1,102	35.7
8-14	417	16.6	473	16.9	465	15.8	577	17.7	499	16.2
15-30	466	18.6	541	19.3	597	20.3	653	20.0	654	21.2
31-89	363	14.5	486	17.3	492	16.8	600	18.4	629	20.4
90+	71	2.8	96	3.4	128	4.4	148	4.5	201	6.5
Cardio-vascular conditions										
1-7	833	29.8	844	27.8	805	26.1	806	25.4	615	22.5
8-14	459	16.4	496	16.3	534	17.3	527	16.6	439	16.0
15-30	687	24.6	694	22.9	723	23.5	728	23.0	637	23.3
31-89	643	23.0	785	25.8	756	24.6	844	26.6	791	28.9
90+	169	6.1	218	7.2	261	8.5	267	8.4	257	9.4

Appendix Figure 2: Time with comorbidity in the six years prior to cancer diagnosis, according to deprivation group



COPD: Chronic obstructive pulmonary disease; dep: deprived

Appendix Figure 3: Number of months with a hospital admission with comorbidity in the six years before cancer diagnosis, according to deprivation group

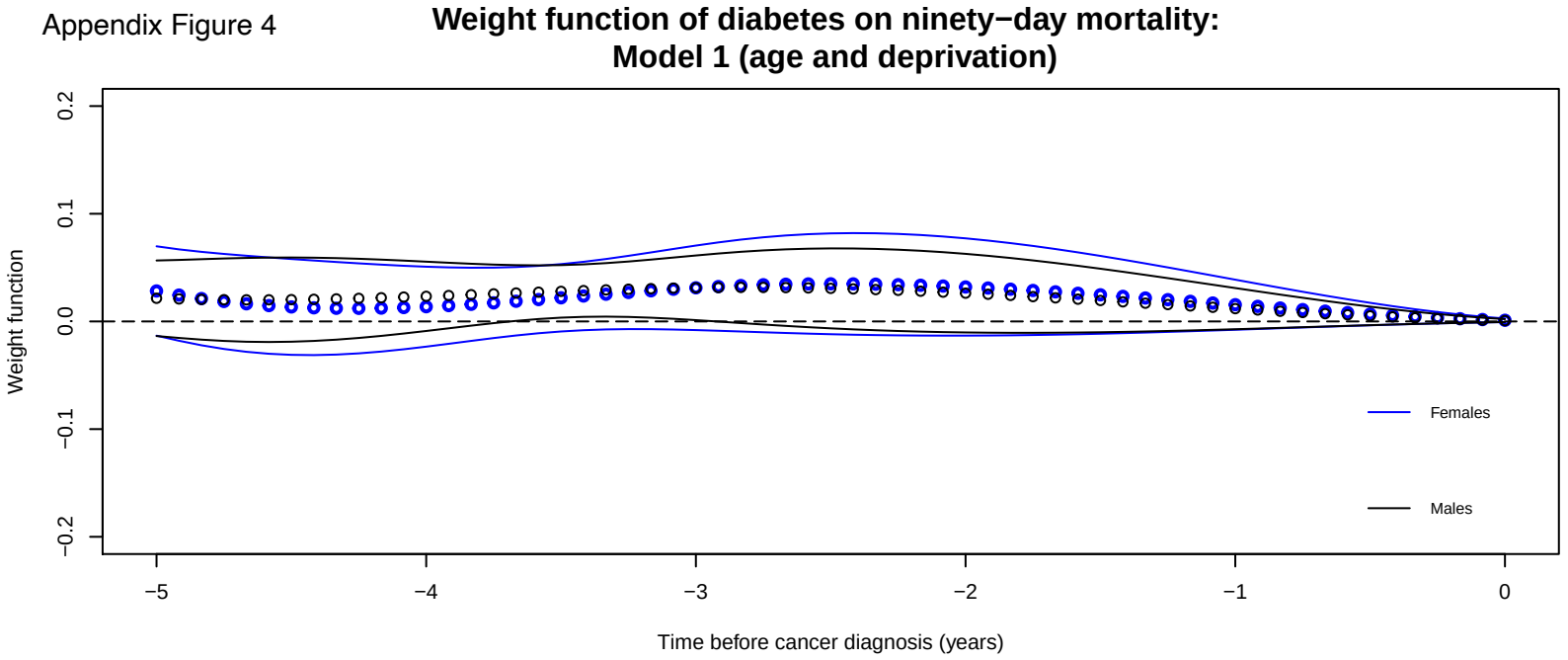


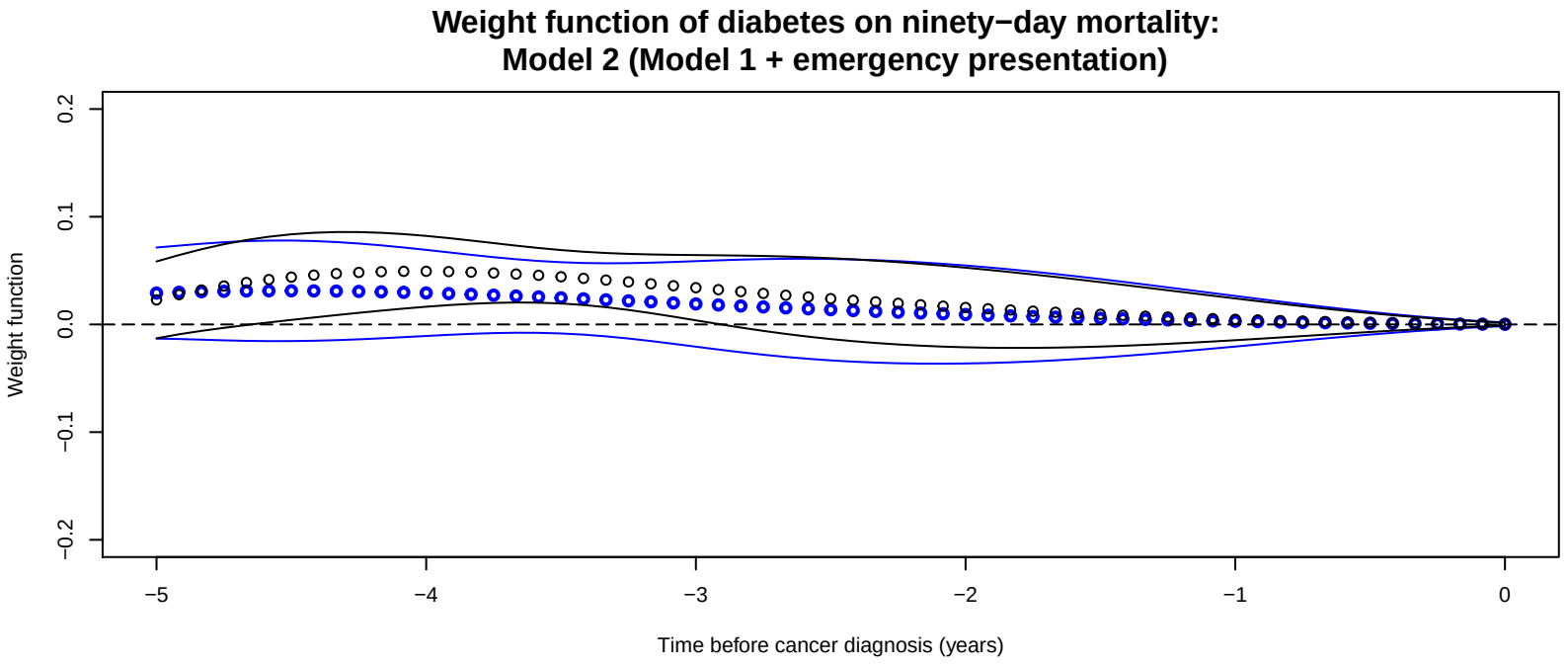
COPD: Chronic obstructive pulmonary disease; dep: deprived

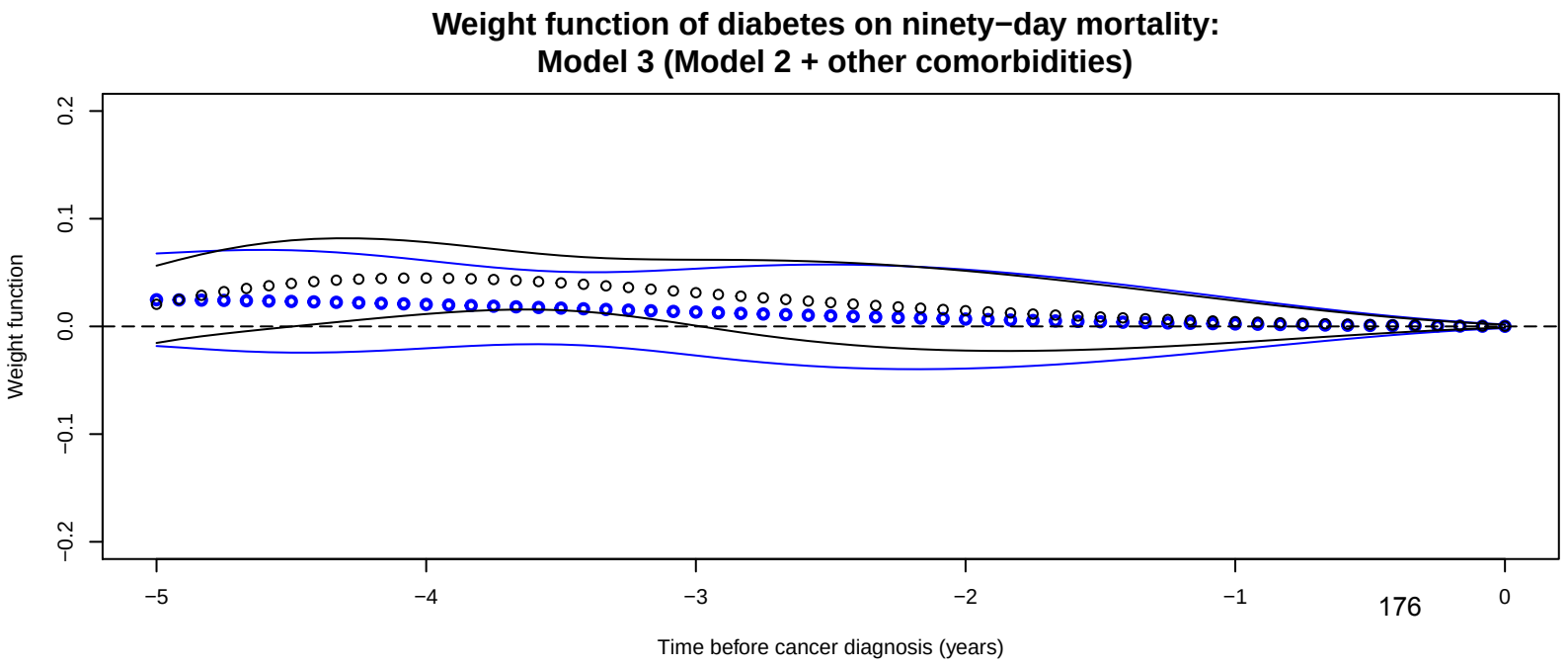
Appendix Table 3: BIC by WCE model and number of internal knots

	Diabetes			COPD			Cardio-vascular conditions		
	Number of internal knots								
	1	2	3	1	2	3	1	2	3
Males									
Model 1	20,194.43	20,200.61	20,208.06	25,175.26	25,179.11	25,185.92	38,141.05	38,146.51	38,154.74
Model 2	19,880.07	19,884.85	19,888.93	24,757.57	24,764.39	24,766.82	37,419.22	37,422.69	37,421.26
Model 3	19,875.90	19,881.82	19,885.54	24,759.03	24,765.91	24,768.39	37,435.60	37,439.60	37,438.31
Females									
Model 1	14,962.74	14,964.93	14,971.97	22,692.38	22,694.77	22,701.79	28,356.25	28,359.66	28,366.93
Model 2	14,678.36	14,684.67	14,690.60	22,291.58	22,298.13	22,304.02	27,795.82	27,801.40	27,806.36
Model 3	14,658.37	14,664.90	14,670.90	22,250.75	22,257.82	22,264.13	27,789.51	27,795.84	27,800.93

Appendix Figure 4

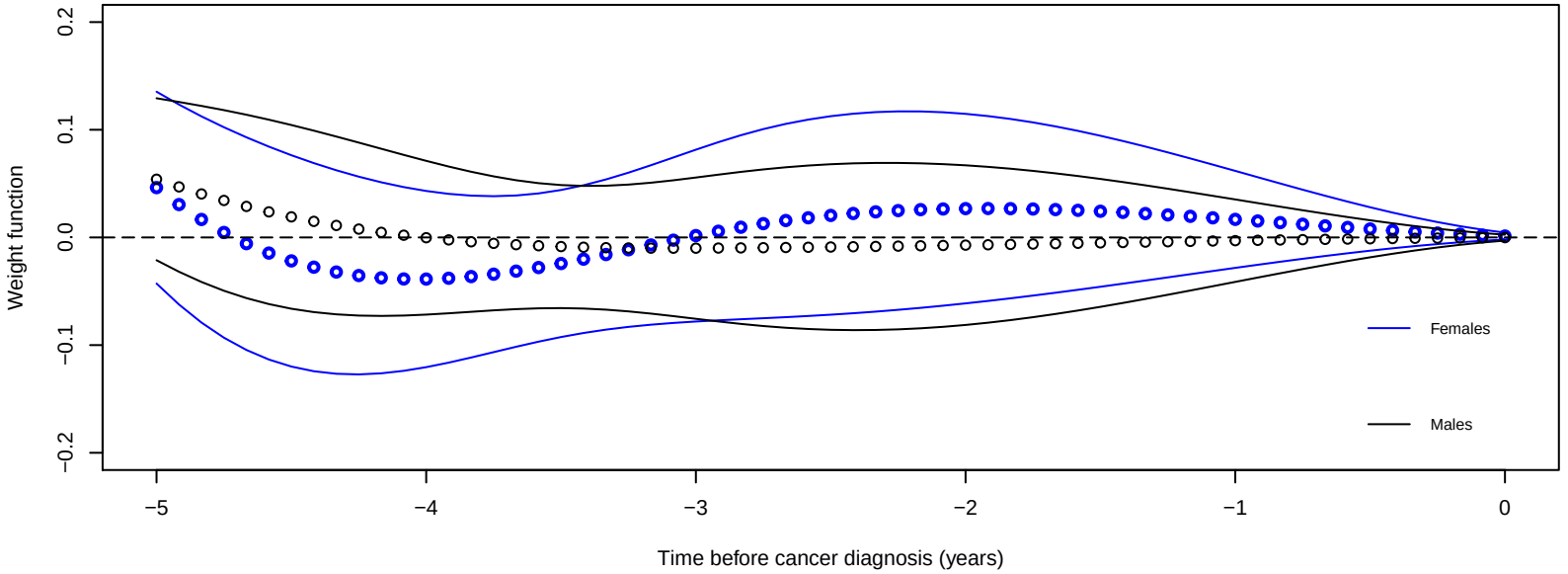




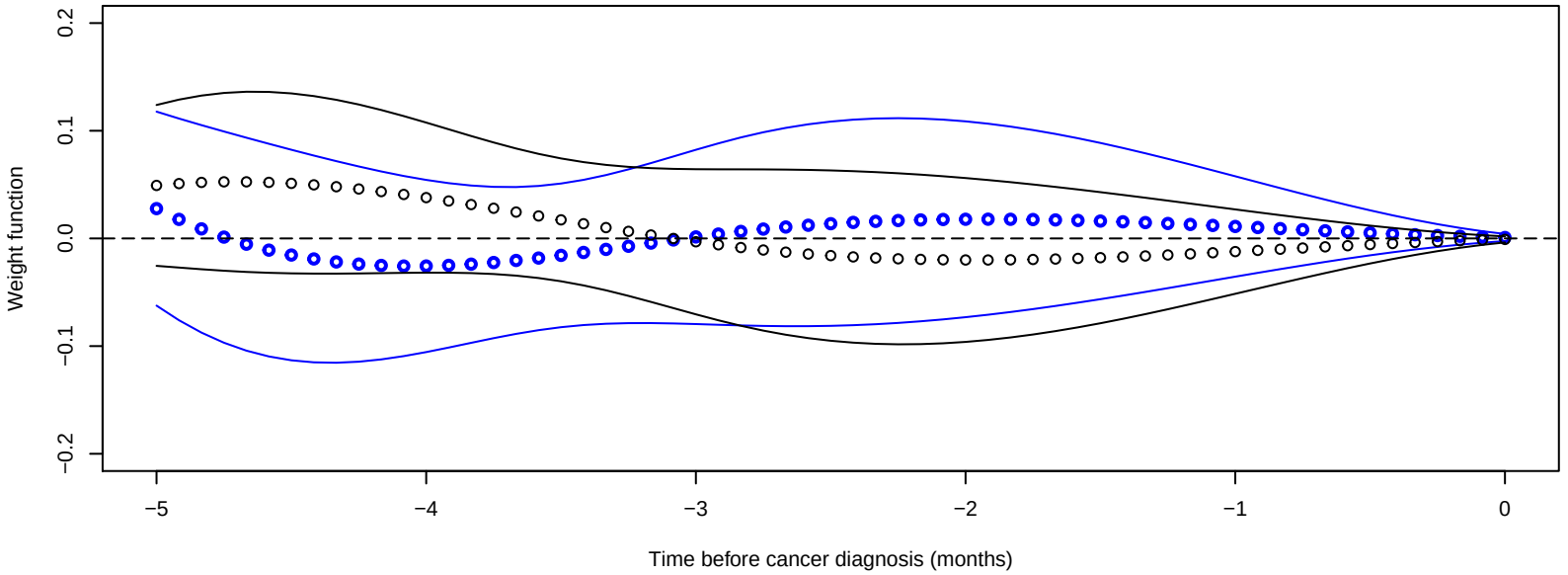


Appendix Figure 5

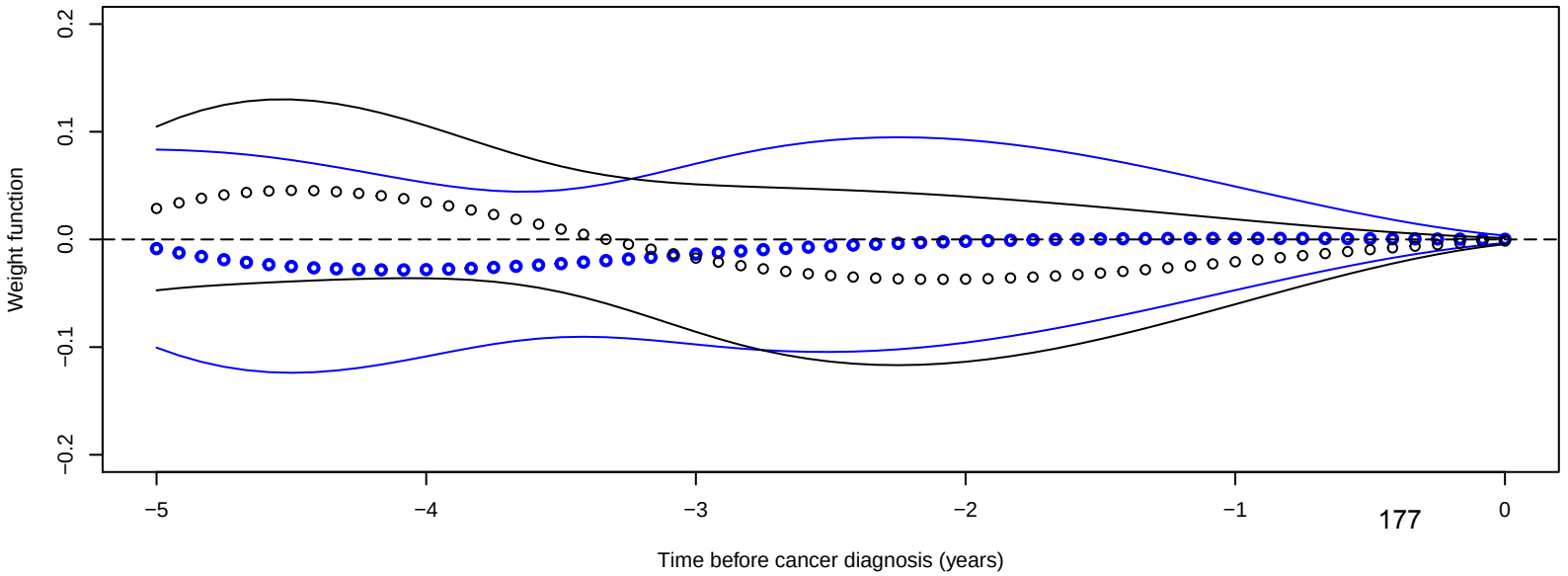
Weight function of COPD on ninety−day mortality:
Model 1 (age and deprivation)



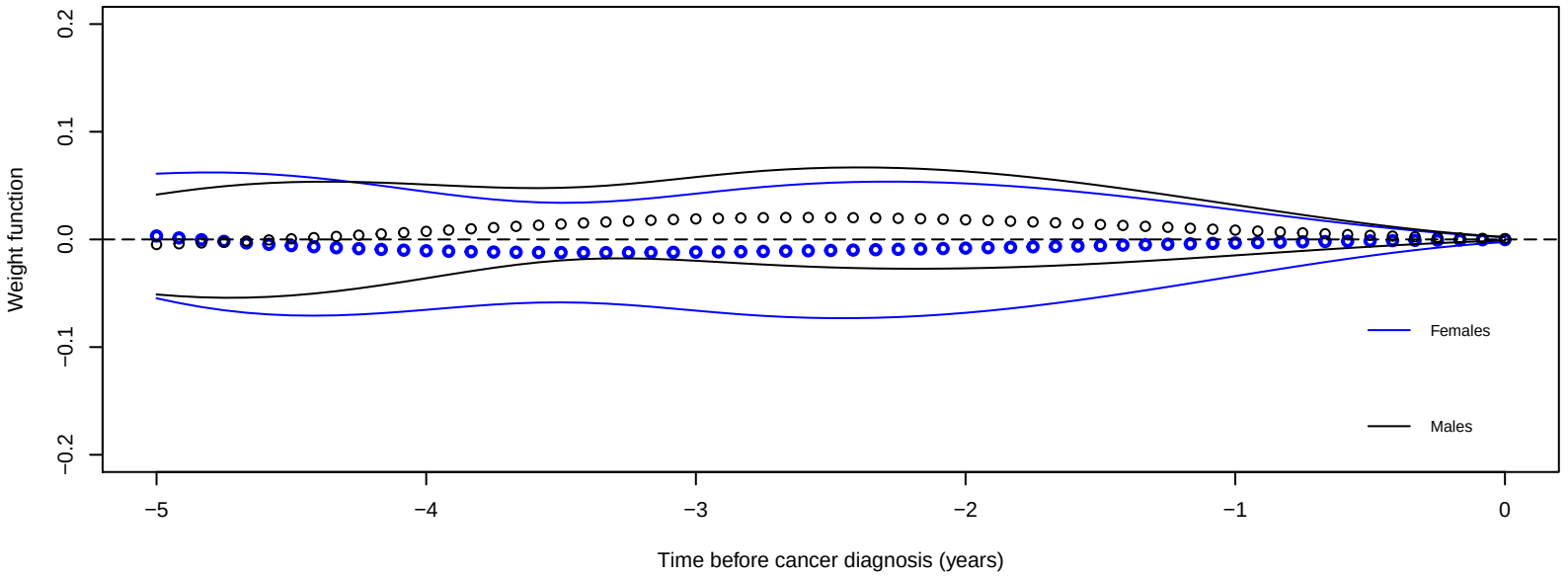
Weight function of COPD on ninety−day mortality:
Model 2 (Model 1 + emergency presentation)



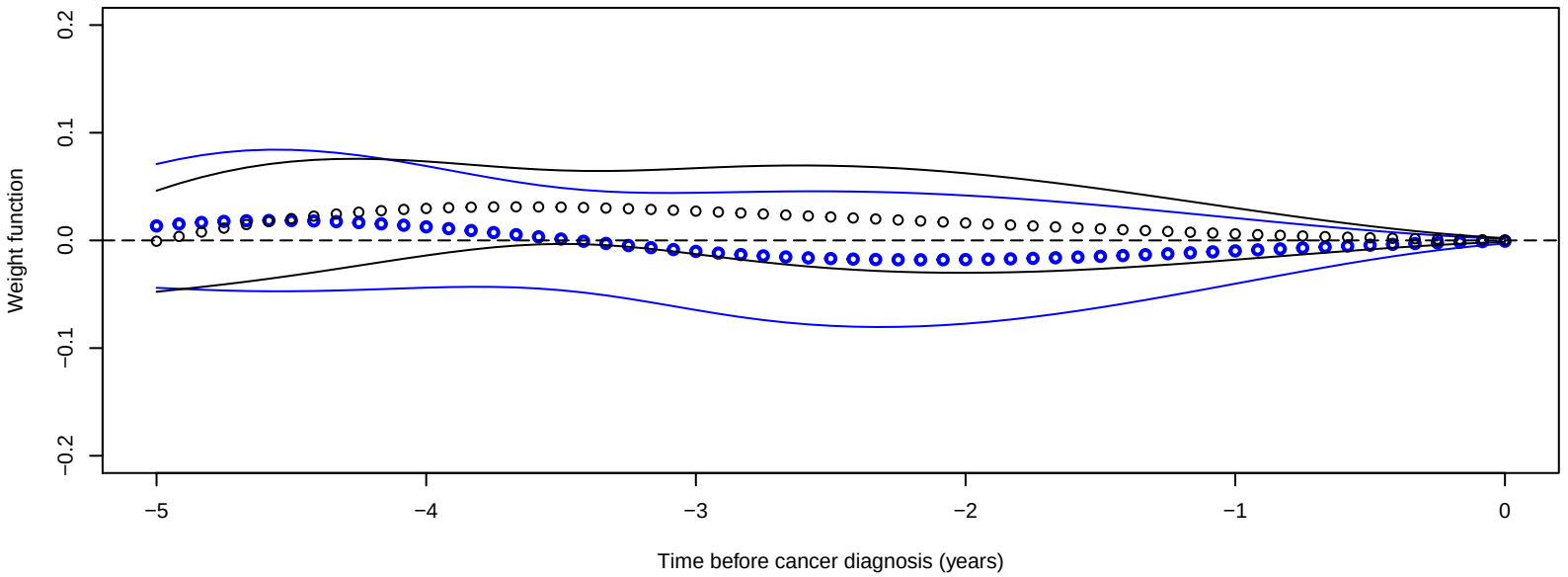
Weight function of COPD on ninety−day mortality:
Model 3 (Model 2 + other comorbidities)



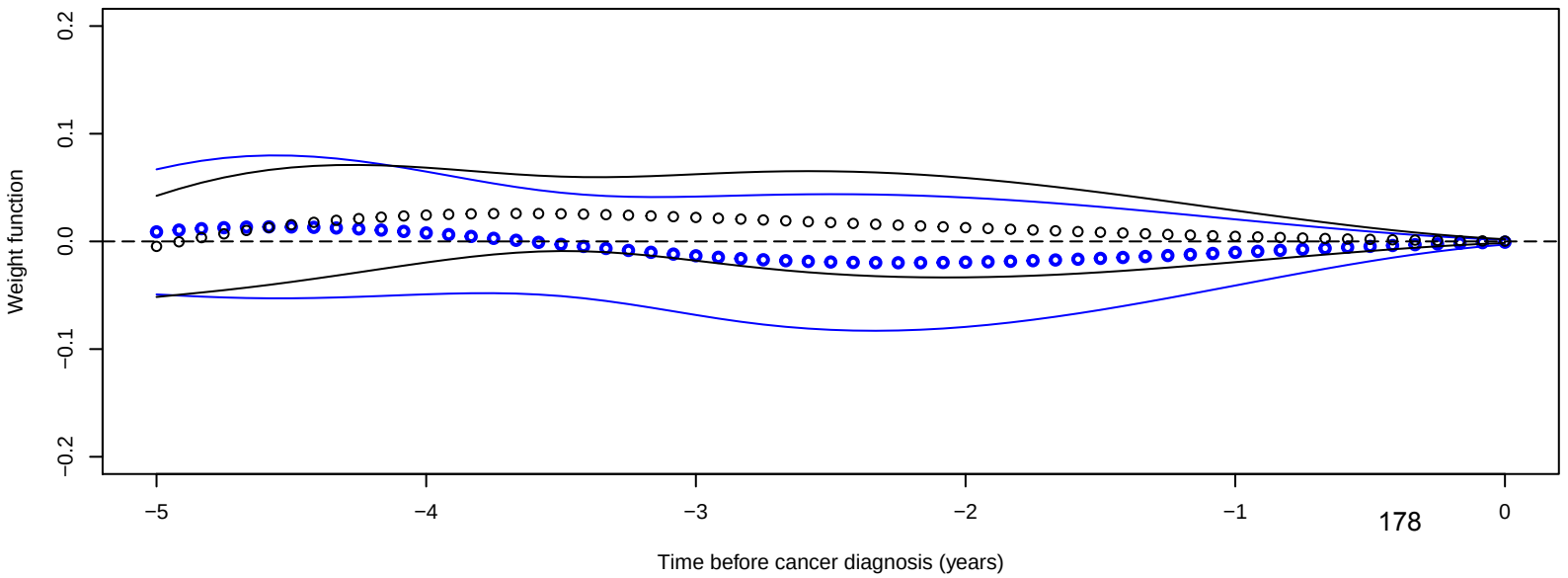
Appendix Figure 6 **Weight function of cardio−vascular conditions on ninety−day mortality: Model 1 (age and deprivation)**



Weight function of cardio−vascular conditions on ninety−day mortality: Model 2 (Model 1 + emergency presentation)



Weight function of cardio−vascular conditions on ninety−day mortality: Model 3 (Model 2 + other comorbidities)



Chapter 6 – Discussion and conclusions

Introduction

In this thesis I have investigated different aspects of comorbidity to better understand its role in socio-economic inequalities in short-term mortality among colon cancer patients in England. I firstly used a summary measure of patient comorbidity (Charlson comorbidity score) to examine comorbidity as one of several prognostic factors in ninety-day mortality. I described comorbidity prevalence among patients with cancer of the colon, rectum or lung or with Hodgkin lymphoma, and examined comorbidity prevalence and multiple comorbidity prevalence according to socio-economic deprivation. To better understand how well information on comorbidity is captured from hospital admissions data I compared prevalence information derived from these data with that from other data sources of chronic disease prevalence. Lastly, I investigated the influence of time living with specific comorbid conditions prior to cancer diagnosis, and the frequency and duration of hospital admissions during this time, on socio-economic inequalities in ninety-day mortality.

In this chapter I discuss each of the research questions of this thesis in turn, summarising the findings and putting them in the context of the existing literature. I then discuss the strengths and limitations of my research. Finally, I discuss the implications of my research findings on healthcare policy and practice and epidemiological research, and offer suggestions for further research.

Prognostic factors in socio-economic inequalities in ninety-day mortality among colon cancer patients

The first research question of this thesis (Research Paper 1)[101] aimed to quantify socio-economic inequalities in ninety-day mortality among patients with colon cancer, and investigate how various

prognostic factors (age and stage at diagnosis, comorbidity, receipt of surgery and presentation for surgery) influence the magnitude of these inequalities.

When I estimated the average predicted probability of death within ninety-days at the deprivation group level, based on the average probability of death of all patients in each group, the most deprived group of patients had a 5-7% higher prediction of death than the least deprived group (depending on the sex of the patient). Further analyses suggested the differential distribution of prognostic factors may explain some of the mortality differences between these groups, with stage and treatment being the strongest contributors to the inequalities.

When investigating the magnitude of the inequalities according to the conditional probability of death (i.e. conditional on specified values of prognostic factors), inequalities were widest among patients receiving an emergency surgery, having an advanced stage of diagnosis or having the highest Charlson comorbidity score (3 or more). Putting this into context, the difference in the predicted deaths of the most versus least deprived groups was less than 1% among 60 year old male patients with a stage 1 diagnosis (irrespective of comorbidity score or surgery received) but as much as 12% among 80 year old male or female patients with a stage 4 diagnosis and the highest comorbidity score who received a major emergency surgery.

There were inequalities in predicted deaths among patients with the highest comorbidity score even for patients with a more favourable, early stage diagnosis who received elective surgery (up to a 2.5% difference in predicted deaths between the most and least deprived such patients). This suggests that there may be aspects of living with or managing comorbidity and multiple comorbidity that more adversely impact the short-term prognosis of the most deprived patients.

Evidence of socio-economic inequalities in the outcomes of colon or colorectal cancer patients are widely reported in the scientific literature[9-12, 57, 211-213] and support the findings of my study. Many

studies have reported on the association between socio-economic position and short-term outcomes, the size of this association varying according to the outcome and the characteristics of the patients studied. For example, among post-operative colorectal cancer patients in England, the most deprived patients had over 30% increased odds of dying within thirty days compared to the least deprived patients.[57] By comparison, among colorectal cancer patients in Granada, Spain, the difference in one-year net-survival (i.e. survival from cancer, after adjusting for expected mortality from other causes) between the most and least deprived patients was 10% among men and 4% among women.[212]

My findings also concur with the evidence from these studies that having a higher burden of comorbidity,[9, 57] a more advanced stage of diagnosis,[57, 212, 213] being of older age,[9, 213] and having an emergency presentation for surgery[9, 57] are associated with poorer patient outcomes.

A strength of my study was that it provided a detailed examination of socio-economic inequalities and how they varied according to different combinations of values of the prognostic factors. This highlighted where vulnerabilities among the most deprived patients lay, and less favourable scenarios for the short-term prognosis of these patients. I was not able to find any other published studies that had explored these inequalities in such a way.

Studies specifically investigating the contribution of comorbidity to inequalities in short-term outcomes of colon or colorectal cancer patients are few. Two studies published by Frederiksen and colleagues reported that adding comorbidity to models adjusted for age, sex, year of operation, alcohol consumption, tobacco smoking and Body Mass Index reduced socio-economic differences in mortality outcomes (thirty-day postoperative mortality[56] or all-cause mortality[52]). A study in the Netherlands reported similar findings.[93]

Based on the findings of my study and the available evidence in the scientific literature, the most deprived patients have poorer short-term prognosis following cancer diagnosis, and comorbidity may play a part in this. Looking at comorbidity in more detail – particularly as pre-existing comorbidities can influence stage at diagnosis[214, 215] and options for treatment[13, 111] - may improve our understanding

of why the most deprived patients with comorbidity fare worse than the least deprived patients with comorbidity.

The prevalence of comorbidity among cancer patients in England

The second research question of this thesis (Research Paper 2)[127] aimed to describe comorbidity prevalence among population-based England cancer registry cohorts of patients with cancer of the colon, rectum, lung or with Hodgkin's lymphoma. I estimated the prevalence of fourteen conditions and the associations between sociodemographic factors and the presence of these conditions among these four cohorts of patients.

Half of the patients in the colon cancer patient cohort had at least one comorbidity, with hypertension, COPD and diabetes being the most common of the fourteen comorbidities studied (age-sex adjusted prevalence of these conditions: 17%, 11% and 6%, respectively). The study showed that increased levels of deprivation were associated with the presence of all of the comorbidities studied except one (rheumatological conditions) among colon cancer patients, and that the most deprived patients had a higher probability of having multiple comorbidities. The majority (70-90%) of colon cancer patients who had conditions such as COPD, diabetes or cardio-vascular conditions (e.g. cerebrovascular disease, congestive heart failure and peripheral vascular disease) also had other comorbidities, suggesting many of these patients may have complex healthcare needs.

My study builds on existing studies of cancer comorbidity prevalence that have reported on the prevalence of conditions among cancer patient cohorts,[48, 116] or provided prevalence estimates according to factors such as patient age and sex.[117] Information in the scientific literature on socio-economic position and comorbidity among cancer patients is more sparse, although a study of cancer patients in the Netherlands reported an association between low socio-economic position and an

increased risk of having cardio-vascular diseases, COPD or diabetes among colorectal cancer patients.[93] Many of the studies that have investigated socio-economic position and comorbidity prevalence are more generally focused on multimorbidity[14, 15, 64, 216] (i.e. the presence of two or more chronic conditions) within the general population, rather than on comorbidity in the context of a primary disease such as cancer. These studies reported that having multimorbidity was more common among people of lower socio-economic position. Looking at chronic diseases in isolation, a recent study using UK data (Whitehall II study linked with Hospital Episode Statistics) reported associations between higher levels of deprivation and conditions such as diabetes, heart failure, chronic obstructive bronchitis, renal failure and liver disease.[217] These associations and that reported in another study of COPD prevalence in England[218] were of a similar magnitude to those reported for the colon cancer patients in my study.

Many of the comorbid colon cancer patients in my study had not just one but multiple comorbidities, and therefore were living with at least three chronic conditions, including cancer. The likelihood of this rose with increasing deprivation and with age. In addition to the implications this may have on the prognosis of these patients at the time of their cancer diagnosis, this also factors into a broader public health issue: the ageing of the population and the rising prevalence of chronic diseases and multimorbidity.[3, 219] Kingston and colleagues predicted that the percentage of the population aged 65 years and older living with four or more health conditions is projected to rise from 10% to 17% between 2015 and 2035.[219] This highlights the importance of healthcare systems that are able to manage the simultaneous care of patients with multiple health conditions, and adapt to an increasing demand on resources.[220] Furthermore, interventions to mitigate the rise in prevalence of chronic diseases (for example, focusing on behavioural and lifestyle risk factors for developing chronic diseases), or interventions to limit the progression of existing conditions and support behavioural self-management of these conditions, may help reduce the prevalence of multimorbidity and the utilisation of healthcare services.

Administrative hospital admissions data as a source of information on chronic disease prevalence

The third research question of the thesis aimed to investigate hospital admissions data in England as a source of information on chronic disease prevalence, by examining how information on the prevalence of thirteen chronic diseases captured from this source compared with prevalence information available from other data sources.

In the first instance, I used hospital admissions data to calculate the crude prevalence of each of the thirteen conditions among an England cancer registry cohort of colorectal cancer patients and compared this with the prevalence among other colorectal cancer patient cohorts reported in the scientific literature. This provided an opportunity to investigate commonly used sources of data on comorbidity among cancer patients. The majority of studies retrieved from the literature search had used administrative data sources to capture information on comorbidity, and patterns in respect to the most prevalent of the thirteen conditions among colorectal cancer patients were consistent among these data sources. Studies of comorbidity among cancer patients in the United States used Medicare claims data to derive information on comorbidity from hospital records and primary care data, which was limited to patients aged 65 years and over. Given the association between increasing age and comorbidity prevalence,[115, 127] it is anticipated that the prevalence of many of the conditions may be higher among this older group of patients than among cohorts of patients that included younger adults. This study also highlighted differences between countries in approaches to obtaining information on cancer comorbidity from healthcare administrative data. Within a universal healthcare system in England, the Hospital Episode Statistics data is collated for all patients admitted to public (National Health Service, NHS) hospitals in the country. These data can be accessed via application to NHS England and can be linked with cancer registration data. In the United States, information on patient hospital records is sourced through health insurance claims (either via public programs such

as Medicare or via private insurers) or via a medical record review.[221] Medicare represents the broadest population-based healthcare administrative data within the United States, representing approximately 97% of patients aged 65 years and over.[222] As discussed earlier in this thesis, after reviewing and evaluating the methods used to define comorbidity among cancer patients in epidemiological studies, Sarfati and colleagues concluded that the different approaches used have varying advantages and disadvantages, but there is no one approach that offers a gold standard to measuring comorbidity among cancer patients.[104] The variety of methods used to measure comorbidity may pose a limitation when amassing evidence-based research upon which to base healthcare policy decisions aimed at improving outcomes of cancer patients with comorbidity. Further inconsistency in the methods of deriving information on comorbidity and differing characteristics of populations upon which the evidence is based may present a further challenge. There has been a call for transparency with - and validation of - algorithms used to identify patients with different health states from routinely collected administrative data, in order to demonstrate accuracy and consistency with the use of these data for this purpose.[223, 224]

The second objective of the study was to compare the age-sex adjusted prevalence among the England cancer registry cohorts of colorectal cancer, lung cancer and Hodgkin lymphoma patients with the reported national prevalence of these conditions among adults in England. National prevalence information, where available, was commonly sourced from data that is taken from a sample of the population rather than being population-based. Data sources included the Health Survey for England (HSE) or the Quality of Outcomes Framework (QOF). These data sources may be subject to biases: survey information may be liable to recall bias or non-response bias and General Practices are offered financial incentives for reporting information on specific conditions through the QOF (reporting bias). National prevalence information was only available for six of the thirteen conditions of interest. The findings suggested that the prevalence of certain conditions (e.g. obesity and diabetes) may be

underestimated from hospital admissions data. Certain conditions sharing common risk factors with cancer, such as COPD, were shown to be more prevalent among the England cancer registry cohorts than among the general population. This was anticipated, but it highlights the problem of comorbidity among cancer patients and more generally, multimorbidity. My findings also showed that the reporting of the prevalence of specific diseases among the general population can be very limited or vary between data sources. Wider disease registration and collection of population-based information on the diagnoses of common chronic conditions would provide a resource with which to monitor changes in incidence and prevalence of these conditions over time, and provide further data resources for epidemiological research into patient outcomes.

Timing and duration of hospital admissions and time with comorbidity as explanatory factors in socio-economic inequalities in ninety-day mortality

The fourth research question of this thesis aimed to investigate socio-economic inequalities in ninety-day mortality among colon cancer patients with comorbidity; specifically, with diabetes, COPD or cardio-vascular conditions (congestive heart failure, myocardial infarction, peripheral vascular disease, or cerebrovascular disease). It also aimed to examine whether time-varying exposure measures of comorbidity (time since a comorbidity was first reported and the duration and timing of hospital admissions during this time), plus other prognostic factors, influence socio-economic inequalities in ninety-day mortality.

This study represented a novel approach to exploring the influence of comorbidity on cancer patient outcomes. I used weighted cumulative exposure models to account for the effect of the time-varying measures of comorbidity on ninety-day mortality. This method, proposed by Sylvestre and

Abrahamowicz,[210] is commonly used in the pharma-epidemiology setting to account for the timing, duration and intensity of drug exposure. Using a more traditional approach to investigate time with comorbidity and time in hospital as exposures on the outcome of ninety-day mortality would have meant summarising these exposure variables and thus removing time-varying information that may be relevant to the association between these exposures and the outcome.

There were inequalities in short-term mortality among each of the subgroups of colon cancer patients with the same pre-existing comorbidity: the most deprived patients with diabetes, COPD or cardio-vascular conditions had an increased hazard of ninety-day mortality compared with the least deprived patients (after adjusting for age and deprivation). After accounting for the time-varying exposure measures of comorbidity, the differences in mortality between the most and least deprived patients reduced within each patient subgroup. The relative reduction ranged from 12% among female patients with one of the cardio-vascular conditions to 68% among male patients with COPD. This finding suggested that, among patients with these pre-existing comorbidities, healthcare utilisation prior to cancer diagnosis may be an explanatory factor in some of the socio-economic disparities in ninety-day mortality after cancer diagnosis. There is evidence to suggest differential patterns in healthcare utilisation between the most and least deprived groups in England. The most deprived groups tend to have more frequent usage or greater need for care due to an increased burden of disease.[225] Indeed, among each of the subgroups of patients I studied, the percentage of the most deprived patients who had lived with the comorbidity in question up to six years and had spent at least 90 days in hospital prior to cancer diagnosis was higher than that of the least deprived patients.

Among patients with COPD, there was an unexpected contrast in findings between male and female patients in respect to socio-economic differences in all-cause ninety-day mortality. After accounting for the time-varying exposure of COPD, and adjusting for age, emergency presentation and the

presence of other comorbidities, there was no evidence to suggest that the most deprived male patients had a higher hazard of mortality than the least deprived male patients. By contrast, the mortality differences between the two deprivation groups persisted among the female patients.

At the onset, socio-economic differences in ninety-day mortality were lower among the male sub-group of patients with COPD: the most deprived patients had a 25% increased age-adjusted hazard of mortality versus the least deprived patients, while among the female sub-group the age-adjusted mortality hazard of the most deprived patients was 71% higher than that of the least deprived patients. After accounting for the time-varying exposure measures of COPD, there was only weak evidence of an 8% increased hazard of mortality among the most versus least deprived male patients, while among the most deprived female patients there was a 60% increased hazard. There is evidence males have a stronger social gradient in mortality from COPD than females,[226] suggesting that these findings relate more to the mechanisms between the existence of COPD and the colon cancer diagnosis (and beyond) than to the presence of COPD alone. The presence of pre-existing comorbidity can influence the stage at which cancer is diagnosed. For example, cancer may be diagnosed at an earlier stage based upon increased contact with healthcare professionals due to the comorbidity, or diagnosis may be delayed where the symptoms of cancer are masked by, or attributed to, the comorbidity.[214, 227] The presence of COPD has been shown to increase the odds of being diagnosed with some cancers at a more advanced stage.[228] There is little information within the scientific literature in respect to socio-economic position and the relationship between healthcare utilisation with COPD and stage of colon cancer diagnosis. It would be useful to investigate this further, to understand if this relationship differs between the most and least deprived patients with COPD, and whether this differs by sex.

Although females tend to have worse COPD outcomes than males,[202, 229] the reasons behind the persistent socio-economic differences in mortality among the female sub-group of patients with COPD

are less clear. Women have a greater vulnerability towards the adverse effects of tobacco smoking than men.[230, 231] As smoking prevalence is associated with higher levels of socio-economic deprivation,[232] the reason for the mortality differences could be related to smoking status, assuming that i) smoking is more prevalent among female than male patients and ii) among the female patients with COPD, smoking is more prevalent amongst the most deprived patients. Having access to data on the smoking status of the patients in this study would have been beneficial, to investigate this more fully.

Another aspect to consider is whether the male and female COPD patient sub-groups studied are equally representative of COPD patients. My analyses focused on colon cancer patients who had COPD recorded in their hospital records up to six years prior to their cancer diagnosis. COPD is a condition that tends to be underdiagnosed, [233, 234] and there is some suggestion that certain clinical guidelines and criteria for the diagnosis of COPD may lead to overdiagnosis of COPD in older men and missed diagnosis of COPD in younger women.[235] An implication of this could be over- and under-representation of COPD patients in the male and female sub-groups of colon cancer patients I studied, respectively. A further implication may be differential severity of disease, where younger female patients may have had more severe disease by the time COPD was diagnosed.[235] There is a possibility of selection bias among the sub-groups of patients I studied, which may have contributed to the unexpected contrast in findings between male and female patients with COPD.

Emergency presentation was a strong prognostic factor in ninety-day mortality among patients with diabetes, COPD or cardio-vascular conditions. Adjusting for emergency presentation with colon cancer and for the presence of multiple comorbidities (factors that are associated with increased levels of deprivation)[127, 236] further reduced the differences in ninety-day mortality between the most and least deprived patients within each of the comorbidity subgroups. However, even after adjusting for these factors the inequalities in ninety-day mortality generally persisted, indicating that other factors appear

to be playing a role in these inequalities. Further investigation of healthcare utilisation prior to cancer diagnosis, according to deprivation group, may provide some insights into the mechanisms that lead to poorer short-term cancer prognosis among the most deprived patients with comorbidity. One dimension of this may be the mechanisms between socio-economic position, comorbidity, stage at diagnosis and receipt of treatment.

Strengths and Limitations

The research conducted for this thesis used population-based cancer registry data, representing a robust and reliable source of information on patients diagnosed with cancer in England. I used multiple linked datasets to supplement the registry data and enhance the range of information available for the cancer patients I studied. These linked data allowed me to obtain information on variables such as presence and timing of comorbidity, stage at diagnosis, surgery received, timing of surgery, presentation for surgery, and the length and frequency of hospital admissions prior to cancer diagnosis.

Comorbidity was the focus of my thesis, and I used the diagnostic fields of hospital admissions data to derive information on comorbidity recorded in the six years prior to diagnosis. I have acknowledged limitations of these data for this purpose in earlier chapters of this thesis, including the possibility of measurement error or misclassification arising when the diagnostic fields are coded from medical notes made by clinicians.[237] Nonetheless, the external validity of the algorithm we developed to extract information on comorbidity was shown to be over 86 percent. [76] My research into sources of information on cancer comorbidity highlighted that routine administrative data such as primary and secondary care records are commonly used as a source of information on cancer comorbidity. These data offer many benefits for epidemiological research, such as being low in cost, accessible, providing

information on a wide range of diseases and offering generalisability due to the large populations they cover.[131]

In the analyses I conducted for the first research question of this thesis (Chapter 3), I had to deal with the problem of missing information for stage at diagnosis among approximately 30 percent of the cohort of colon cancer patients. However, as stage appeared to be missing under the Missing at Random mechanism, it was possible to undertake multiple imputation of these data and avoid the biases associated with a complete case analysis.[238] Missing at Random is the mechanism whereby the propensity for information to be missing is not related to the missing data but is related to some of the observed data.[238] A challenge that I faced with this process was that the analysis model I developed to address my research question was not compatible with imputation models used in traditional approaches to multiple imputation. This was because the analysis model included interactions between stage and other covariates (which could not be included in an imputation model) and age at diagnosis was modelled using a cubic spline to investigate the non-linear effect of age on the outcome of ninety-day mortality. To overcome this problem I used the Substantive Model Compatible Fully Conditional Specification approach to multiple imputation, which has been shown to produce consistent estimates for analysis models which include non-linear covariate effects or interactions.[239] A further benefit of this was that it provided me with an opportunity to broaden my experience with the use of multiple imputation.

My research used the Income Deprivation domain of the England Indices of Multiple Deprivation (IMD) 2010 as a measure of socio-economic position. This is an ecological measure of deprivation at the small area level, and provides an approximate summary of income deprivation of individuals living within each area. It reflects a mixture of individual and contextual deprivation, and can highlight areas in which disadvantage may be concentrated.[240] However, it does not fully represent the income deprivation status of all individuals, and therefore cannot be considered as a surrogate for individual deprivation.[241]

The aim of my thesis was to investigate the role of comorbidity in socio-economic inequalities in ninety-day mortality among colon cancer patients. A limitation of the data I used for this research is that it did not provide information on detrimental lifestyle or behavioural factors that are more prevalent among the most deprived groups, are risk factors for some of the chronic conditions I studied as comorbidities (e.g. COPD or diabetes) and are associated with early mortality. Examples of such factors include tobacco smoking status, alcohol consumption, poor dietary habits and lack of physical activity. In my research the outcome of interest was all-cause ninety-day mortality, meaning that comorbid patients could have died from complications of their comorbidity or other reasons, rather than directly due to their cancer. Lifestyle factors such as tobacco smoking and poor diet are unlikely to confound the relationship between socio-economic position and all-cause ninety-day mortality, as it can be argued that they are on the causal pathway. For example, increased deprivation levels lead to increased prevalence of smoking, while smoking is associated with increased risk of mortality.

The relationship between socio-economic position and increased short-term mortality following colon cancer diagnosis is complex, given that many prognostic factors in short-term mortality are also associated with socio-economic position, such as later stage at diagnosis,[213] diagnosis via emergency presentation[242] and increased comorbidity burden.[127] An additional dimension to this relationship is provided by other variables associated with socio-economic position that can influence cancer diagnosis and prognosis. For example, the level of social support available to a patient or their beliefs about cancer risk or screening have been shown to be associated with lower uptake in routine cancer screening among people of lower socio-economic position.[243] Barriers to presentation with cancer symptoms, such as lack of recognition of common symptoms or difficulties travelling to medical appointments, are more common among people living in more deprived areas.[244] Furthermore, patient socio-economic position can influence clinical management decisions of physicians.[245]

My research considered comorbidities that had existed up to six years prior to cancer diagnosis, while patient deprivation group was based upon residential postcode at the time of cancer diagnosis. My research showed that the more deprived patients were more likely to have comorbidity.[127] It is possible that the presence of pre-existing health conditions could influence the deprivation group patients are assigned to at cancer diagnosis. For example, a long-term health condition may prevent or limit the ability to undertake employment, which in turn could impact upon level of income and area of residence. However, as the presence of many common conditions is associated with lower socio-economic position,[218, 246, 247] this scenario may be more likely to arise among people who are already experiencing some income deprivation, suggesting the effect on socio-economic position may be small. Another aspect of living with a long-term health condition that could influence income deprivation is the cost of treatment for the condition. Receiving treatment for a health condition is unlikely to have a substantial impact on income deprivation in England, where there is government-funded universal healthcare free at the point of use. However, in countries where universal public healthcare is not available, medical debt (i.e. problems paying medical bills) from treatment for chronic health conditions can in some instances cause financial hardship.[248] There is some evidence within the United States that medical debt may impact upon ability to access needed care,[249] suggesting that in such scenarios medical debt (and financial hardship) could be a potential mediator in the relationship between pre-existing health conditions and cancer.

As my research investigated the influence of pre-existing comorbidity on ninety-day mortality following colon cancer diagnosis, it would have been useful to have information on other measures of patient health status. One such example would be patient performance status, which is a measure of health status represented by a score within a scale that defines a patient's ability to perform certain activities of daily living (Appendix Table 4).[250]

The data I used were data of patients diagnosed with cancer between 2009 until 2013, thus my research is based on patients diagnosed with cancer between 7 and 11 years ago. While these do not represent the most recent data, other studies of cancer outcomes including patients with more recent diagnoses of cancer are still reporting the existence of socio-economic inequalities.[251, 252] The findings of my research are therefore still applicable to the current time.

Implications of this research

Health policy and practice

Socio-economic position, multimorbidity and healthcare utilisation

The findings of research highlighted the greater burden of comorbidity among the most deprived patients. I investigated pre-existing comorbidities recorded up to six years prior to cancer diagnosis, which meant that patients could have been living with these conditions for some time prior to being diagnosed with cancer. Within the context of existing evidence, these finding suggest that, even before the time of cancer diagnosis, the most deprived patients with comorbidity may already have complex healthcare needs as compared with the least deprived patients, particularly those patients with multiple comorbidities.

Low socio-economic position is associated with an increased risk of adverse outcomes from several of the chronic conditions I studied as comorbidities. For example, COPD patients of lower educational attainment and household income tended to have a greater risk of more severe disease, poorer lung function and physical functional limitations,[253] while low socio-economic position is associated with an increased risk of cardiovascular disease mortality,[254] a higher risk of readmission to hospital following a previous admission related to heart failure,[255] and a higher rate of hospitalisation for COPD complications.[256]

Furthermore, having multiple chronic conditions, or multimorbidity, is associated with a variety of outcomes including increased mortality and poorer quality of life,[257, 258] poor functional status and adverse drug events.[259] Patients with multimorbidity tend to have higher rates of healthcare utilisation.[260-263] For example, patients with multimorbidity may have up to 2.5 times the GP consultations or hospital admissions of patients without multimorbidity.[264] Moreover, a socio-economic gradient has been reported in respect to healthcare utilisation among multimorbid

patients,[225] with the most deprived having a larger number of healthcare consultations, hospital admissions, longer hospital stays[265-267] and unplanned admissions.[268] General practitioners managing multimorbid patients in deprived areas of Scotland reported the needs of their patients as complicated and challenging, particularly where patients were dealing with difficult social and financial problems in addition to their health.[269]

There is evidence within some healthcare systems that organisational interventions can improve outcomes among multimorbid patients.[270] For example, a study conducted in the United States showed that coordination of care between primary care physicians, nurses and social workers involving a set of defined intervention activities for chronically ill older patients (home visits, formulation of a risk reduction plan, maintaining contact with the patient for monitoring purposes) led to a reduction in healthcare utilisation.[271] Organisational interventions aimed at management of particular risk factors (such as healthcare utilisation) or areas where patients face challenges have been reported as being the most effective.[270] Implementation of interventions offering broader-based support to patients with multimorbidity in deprived areas may help improve outcomes of the most deprived cancer patients with comorbidity or multiple comorbidities.

Socio-economic position and stage of cancer diagnosis among patients with pre-existing comorbidities

While low socio-economic position has been linked with increased comorbidity burden among cancer patients,[93, 127] it is also associated with advanced stage of cancer at diagnosis.[213] The relationship between comorbidity and cancer stage is complex: the presence of comorbidity may delay diagnosis due to masking cancer symptoms or interfering with diagnostic investigations[128] or alternatively, result in an earlier diagnosis because of more frequent healthcare-seeking with the comorbidity.[214, 227] Studies in England have shown that the management of certain conditions, such as hypertension, may provide an opportunity for potential cancer symptoms to be discussed by patients or discovered by doctors and lead to an earlier cancer diagnosis.[128, 272] Another study of patients with one of nine

different types of cancer (breast, colon, rectum, liver, stomach, ovary, uterus, bladder or kidney) reported evidence that having diabetes with complications increased the odds for an early stage of cancer diagnosis by approximately 24% but also increased the odds of unknown stage by approximately 30%.[228]

Diabetes is a known risk factor for developing colorectal cancers.[31] In the United States, several studies have been conducted in the last two decades that investigate uptake of colorectal cancer screening among people with diabetes. Results of these studies have been mixed: one found that people with diabetes were not much more likely to receive screening than people without diabetes,[273] while one reported that women with diabetes had 14% higher odds of receiving colorectal cancer screening than the women without.[274] Another study in the United States reported that 39% of adults with diabetes were not up to date with the guideline-recommended colorectal cancer screening.[275] Similarly, a recent study in England found that approximately 40% of adults with type 2 diabetes were not up-to-date with their biennial colorectal cancer screening invitation.[276]

The bowel screening programme in England is currently aimed at men and women aged 50-74 years. Uptake of colorectal cancer screening in England tends to be socially graded,[277] for example, a 43% versus 57% uptake was reported among the most versus least deprived groups between 2010 and 2015.[278] Earlier research concluded that factors such as lack of social support and beliefs about cancer risk and screening may influence this social gradient.[243] To address this, initiatives such as implementation of a colorectal health promotion campaign and targeted screening programme may be a practical step in aiming to detect colorectal cancer earlier among high risk groups or people within the screening age range living in deprived areas.

Management of patients with multiple chronic diseases in the healthcare system

Healthcare systems such as the National Health Service have historically tended to be based around single disease management, with highly specialized secondary care services. As a result, patients with

multiple chronic conditions and more complex healthcare needs often receive duplicative and fragmented care.[63, 279] In a study published in 2013, Hughes and colleagues reviewed five clinical guidelines of the UK's National Institute of Health and Clinical Excellence (NICE) – an advisory body in the domain of health, public health and social care. They chose guidelines for five conditions that are common comorbidities. Their research found that comorbidity was inconsistently accounted for in these guidelines, ranging from being discussed extensively to not being mentioned at all.[280] Furthermore, patient centred care was discussed only in a generic context with limited recommendations for clinicians.[280]

The consensus of opinion in the scientific literature advocates for a change in focus from treating single diseases to person-centred approaches to enable more effective management of people with multimorbidity.[4, 64, 69, 279-282] A more optimal health care delivery would include integration and coordination across conditions as well as between clinicians and settings,[69] and take factors such as patient age and socio-economic position into account.[264] More recently in the UK there have been plans to move towards a more integrated care approach within the NHS. The NHS Five Year Forward View published in 2014 pledged to pledged to reduce barriers in the provision of care between different healthcare providers, for example, by delivering some services in specialist centres organised to support people with multiple health conditions as well as those with single diseases.[283]

Given that certain chronic conditions share common risk factors with cancer, including older age, specialist centres that provide a multi-disciplinary approach to treating cancer alongside specific comorbidities may improve patient outcomes. For example, the common co-existence of cancer and cardiovascular diseases,[284] and the complexities of managing both conditions at the same time,[285] has led to the establishment of 'cardio-oncology' services in some NHS hospitals in England.

The impact of COVID-19 on cancer patients, diagnostic services and cancer care

The COVID-19 epidemic in the United Kingdom has impacted the healthcare system and the delivery of cancer care. At the time when the United Kingdom went into lockdown in March 2020, the healthcare provided by the National Health Service switched to being almost entirely focused on caring for patients with COVID-19. One impact of this has been some delays in patients being diagnosed with cancer. Because of measures put in place to restrict the spread of coronavirus, less face-to-face primary care consultations were taking place, and fewer urgent referrals to specialists for investigation of cancer symptoms (the "2-Week-Wait" referral pathway) were being made.[286] The impact of delays in colorectal cancer diagnosis via the 2-week-wait pathway over a three-month lockdown has been predicted as a 10-16% reduction in 10-year net survival (depending on age group), equating to 981 lives lost.[287] A further implication of the impact of COVID-19 on the healthcare system was that elective surgeries were suspended,[288] which delayed many cancer surgeries. It has been predicted that a six-month delay in surgery for cancer of the colon or rectosigmoid junction would reduce 5-year net survival by up to 5% among patients with a stage 1 diagnosis and up to 30% among patients with a stage 3 diagnosis, depending on the age of the patient.[289]

Cancer patients are vulnerable to COVID-19 infection as they are in an immunosuppressive state due to their malignancy and anticancer treatments.[290] Moreover, cancer patients with comorbidity may also be at a greater risk of complications with COVID-19 due to their additional disease(s). COVID-19 infection has led to increased COPD severity and mortality among people with COPD,[291] while diabetes is a risk factor for poorer prognosis following infection with COVID-19.[292] To date there is limited research on the impact of deprivation on the outcomes of cancer patients with a COVID-19 infection. However, more generally, an article currently under peer review reports a 2% increase in the COVID-19 mortality rate for each percentage point increase in the proportion of the population in England experiencing income deprivation.[293]

The scientific evidence on the influence of the COVID-19 pandemic on cancer patient outcomes continues to grow. It is not yet known if the most deprived cancer patients have been more adversely impacted by the COVID-19 pandemic than the less deprived patients. However, the most deprived cancer patients with comorbidity and multiple comorbidities are likely to be among the groups most vulnerable to adverse outcomes following COVID-19 infection. The challenge for healthcare providers will be to protect these groups while ensuring continuation with their cancer care.

Points for consideration by health policy makers and health service managers

The findings of this research may be useful to health policy makers and health service managers, specifically when drafting guidelines or policy focused on mitigating inequalities in access to health care and inequalities in health outcomes. Table 6.1 summarises points for consideration.

Table 6-1 Points for consideration by health policy makers and health service managers

Finding	**For consideration**
Higher prevalence of comorbidity and multiple comorbidity among the most deprived cancer patients	Clinical guidelines include clear advice on dealing with common comorbidities, and on managing common concomitant conditions in parallel.
	Multi-disciplinary approach for the management of cancer with other chronic conditions, to improve outcomes among multimorbid cancer patients.
	Targeted interventions to reduce prevalence of chronic disease / development of further chronic diseases among at-risk patients living in deprived areas, for example, smoking cessation programmes.
	Support for patients with chronic health conditions who are living with mental health conditions or facing social challenges that may compromise their ability to manage their (physical) health (e.g. supporting patients in tandem with Adult Social Care teams).
Stage at diagnosis and surgical treatment received may contribute towards socio-economic inequalities in short-term mortality among colon cancer patients	Targeted screening for those clinically at risk of developing colorectal cancer / with existing chronic conditions / from deprived areas, to facilitate earlier cancer diagnosis and improved prognosis
	Targeted health promotion campaigns to raise awareness of bowel cancer health and cancer symptoms
	Policy focused on ensuring equality in access to health care, specifically in regard to: ▪ Access to specialised clinicians / surgeons ▪ Support provided following cancer diagnosis and in preparation for treatment ▪ Availability of post-operative care facilities and quality of post-operative care
Comorbidity-specific socio-economic inequalities in short term mortality following colon cancer diagnosis	Healthcare usage of the most deprived patients with pre-existing chronic diseases provides opportunity for early discussion of cancer symptoms, and for early detection – e.g. via targeted screening (see above)

Epidemiological research

Benefit of wider registration of common chronic diseases in England

A finding of my research was that there was limited publicly available information on the English national prevalence of several of the chronic conditions I studied, either from government sources or within the scientific literature. Moreover, certain comorbidities that I studied, such as diabetes, may be underreported in hospital admissions data - a commonly used source of information on comorbidity. The World Health Organisation advocates for patient registries in disease management, to facilitate the provision of the necessary continuity of care for chronic diseases.[294] Registries also facilitate public reporting and retrospective or prospective research,[295] and have been shown to improve patient outcomes and processes of care.[295-297]

When conducting epidemiological studies of comorbidity among cancer patients, it would be beneficial to have access to data from population-based disease registries to capture information on co-existent diseases among patients. This would provide a comprehensive source of information on specific chronic conditions and provide details that it may not be possible to verify from administrative data (for example, date of diagnosis). These data can also be used to validate the prevalence information captured in administrative data sources. Wider registration of common chronic diseases and accessibility to the data collated would facilitate more detailed epidemiological investigations into the outcomes of cancer patients living with specific comorbid conditions.

Next steps and suggested further research

The findings of my research suggested that healthcare utilisation prior to cancer diagnosis may have contributed toward socio-economic differences in ninety-day mortality among patients with pre-existing diabetes, COPD or cardio-vascular comorbidities. Further research into patterns in hospital healthcare utilisation with these and other pre-existing comorbidities, according to deprivation group and stage of cancer diagnosis, may help to unravel the mechanisms behind these findings. In particular, it would be useful to ascertain whether there are differential patterns in healthcare utilisation and in availability of resources, whether time spent in hospital with pre-existing conditions is influential in the stage at which cancer is diagnosed and the treatment received following cancer diagnosis, and whether this differs according to deprivation group.

My research focused on physical comorbidities among cancer patients. Research to investigate the influence of mental comorbidities, either alone or in combination with physical comorbidities, may help to further disentangle the role of comorbidity in socio-economic inequalities in cancer outcomes. Studies of patients in Scotland highlighted that mental-physical multimorbidity was common,[264] associated with socio-economic deprivation,[64] and that this combination of co-existing conditions presented the biggest burden to the most deprived patients in terms of managing their own health.[269]

Further research examining longer-term outcomes of cancer patients may also be insightful in better understanding the mechanism between comorbidity, socio-economic position and cancer prognosis. While socio-economic inequalities in mortality tend to be more evident in the short-term after cancer diagnosis[12] it would be interesting to understand whether these inequalities persist longer-term among patients living with specific comorbid conditions.

Conclusions

The role of comorbidity in socio-economic inequalities in short-term mortality among colon cancer patients is complex. Using cancer registry data linked with other population-based data sources I was able to examine different dimensions of comorbidity and its relationship to socio-economic position and short-term mortality among colon cancer patients.

My research emphasised the increased burden of comorbidity among the most deprived cancer patients. I have shown an association between increased levels of deprivation and the prevalence of most of the comorbid conditions I studied, and the prevalence of multiple comorbidity. This study added to the existing scientific literature by exploring the associations between sociodemographic factors and the prevalence of specific comorbidities among four large population-based cohorts of cancer patients in England.

The results of my research showed that the most deprived colon cancer patients consistently had poorer short-term mortality then the least deprived patients, even after adjusting for patient age, stage at diagnosis, Charlson comorbidity score and receipt and presentation for surgical treatment.

Inequalities in ninety-day mortality were evident among patients with the same levels of comorbidity. Among patients with the higher Charlson comorbidity score the magnitude of the inequalities was influenced by the status of other prognostic factors, widening with advanced stage, age and receiving emergency surgery. This suggested that some (potentially unmeasured) aspect of living with or managing comorbidity or the cancer was leading to more adverse short-term outcomes for the most deprived patients.

Exploring this further by examining comorbidity at a more granular level, my findings suggested that accounting for time with a specific comorbidity and differential patterns in healthcare utilisation prior

to cancer diagnosis reduced some of the differences in ninety-day mortality between the most and least deprived groups of colon cancer patients with diabetes, COPD or cardio-vascular conditions. This may possibly reflect greater comorbidity severity or more complex healthcare needs among the most deprived patients. However, even after accounting for the presence of comorbidity and other dimensions of living with a comorbidity prior to cancer diagnosis, the socio-economic inequalities in ninety-day mortality among comorbid patients persisted. These findings suggested other factors, rather than the direct influence of comorbidity, may be contributing towards these inequalities.

The growing prevalence of multimorbidity and the burden of comorbidity among cancer patients highlights the need for healthcare systems designed and equipped to manage multiple chronic conditions simultaneously. Undertaking a multi-disciplinary approach to treating cancer alongside other chronic diseases may improve treatment options and outcomes of the most deprived patients, who are those most likely to be living with comorbidity or multiple comorbidity.

Further investigation of hospital healthcare utilisation according to patient deprivation group may provide insights into opportunities to improve outcomes of the more deprived groups living with chronic diseases who go on to develop colon cancer. Mechanisms to be explored include the interplay between deprivation, pre-existing chronic disease(s), stage at cancer diagnosis and options for treatment of cancer. One example of this would be targeted colorectal cancer screening of at-risk and disadvantaged groups seeking healthcare for specific chronic diseases, to facilitate earlier stage cancer diagnosis and thus improved prognosis.

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Appendices

Appendix Table 1 - The prevalence (%) of thirteen comorbid conditions among colorectal cancer patient cohorts identified from the scientific literature

Appendix Table 2 – The reported prevalence of thirteen health conditions in England or the United Kingdom

Appendix Table 3 – The crude and age-sex adjusted prevalence (%) of thirteen condition health conditions among patients diagnosed with colorectal cancer, lung cancer or Hodgkin Lymphoma in England from 2009-2013

Appendix Table 4 – Performance Status Scales (the Zubrod Scale and the Karnofsky Scale)

Appendix Figure 1 – Flow diagram to show the process followed by the stage algorithm to derive the overall grouped TNM stage at diagnosis variable, based upon individual components of tumour (T), nodes (N) and metastases (M)

Appendix A: The domains of the England Indices of Multiple Deprivation 2010

Appendix B: Presentations at national and international conferences

Appendix Table 1: The prevalence (%) of thirteen comorbid conditions among colorectal cancer patient cohorts identified from the scientific literature

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Liver disease									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	1.4%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	Mild liver disease: 0.6% Moderate / severe liver disease: <0.1%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Moderate / severe liver disease Colon: 1.7% Rectal: 0.7%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	Mild liver disease: 1.6% Moderate / severe liver disease: 0.9%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	Mild liver disease: 0.3% Moderate / severe liver disease: 0.2%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	5.3%
Diabetes									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	17.8%
Frederiksen et al. 2009	Denmark	Retrospective cohort	Colorectal	2001-2004	Patients diagnosed with adenocarcinoma of the colon or rectum in Denmark	Hospital records and files of the Register of Medicinal Product Statistics, which contains information on the sales of pharmaceutical products in Denmark	8,763	Median age 69 years, interquartile range 61-76 years	8.0%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	Diabetes (without chronic complication): 2.7% Diabetes with chronic complications: 0.2%
Aggarwal et al. 2013	Rochester, United States	Retrospective cohort	Colorectal	2007	Patients of Mayo Clinic	Medical records	100	Range not reported, mean 71.6 (+/-9.4) years	19.0%
Ahmadi et al. 2014	Iran	Prospective cohort	Colorectal	2006-2011	Patients from 10 gastrointestinal clinics	Blood test for Type 2 Diabetes at time of enrollment	1,127	Range not reported, mean 53.4 (+/-14.3) years	8.7% (95%CI: 7.0-10.7%)
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Diabetes (uncomplicated) Colon: 5.9% Rectal: 4.7% Diabetes with complications Colon: 5.0%

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Ramjeesingh et al. 2016	Southeastern Ontario, Canada	Retrospective cohort	Colorectal	2005-2011	Patients treated at a Cancer Centre	Diabetes treatment information in patient oncology consult notes	1,304	24-98 years, median 71.2 years	21.2%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	Diabetes (without end-organ damage): 16.1% Diabetes (with end-organ damage): 1.0%
Cuthbert et al. 2018	Alberta, Canada	Cohort	Colorectal	2004-2015	Patients recorded in cancer registry data	Inpatient hospital data and physician billing claims	12,265	Range not reported, mean 71.6 (+/-9.4) years	14.0%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	Diabetes (uncomplicated): 18.8% Diabetes with complications: 4.9%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded > 6 months prior to cancer diagnosis)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	23.6%
Obesity									
Haydon et al. 2006	Australia	Prospective cohort	Colorectal	1990-2002	Melbourne Collaborative Cohort Study participants diagnosed with colorectal cancer between recruitment and August 2002	Body measurements at time of recruitment to study	526	42-79 years, median 66.8 years	Body mass index >30: 24%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	0.4%
Yang et al. 2012	United States (California, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, Rural Georgia, Kentucky, Louisiana, New Jersey)	Retrospective cohort	Colon	1999 - 2004	Patients recorded in cancer registry data	Medicare claims from 12 months before to 3 months after cancer diagnosis	36,079	66+ years	4.3%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Colon: 1.9% Rectal: 1.8%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	2.0%
Dementia									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	3.2%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	1.0%

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Colon: 1.8% Rectal: 1.4%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	0.6%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	1.7%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	4.5%
Hemiplegia or paraplegia									
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	0.8%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Paralysis Colon: 2.3% Rectal: 1.5%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	0.3%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	0.5%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	0.3%
Cerebrovascular disease									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	10.3%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	2.9%
Ahmadi et al. 2014	Iran	Prospective cohort	Colorectal	2006-2011	Patients from 10 gastrointestinal clinics	Test for hypertension at time of enrollment	1,127	Range not reported, mean 53.4 (+/-14.3) years	13.4% (95%CI: 11.1-15.8%)
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Colon: 5.1% Rectal: 3.8%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	2.3%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	6.0%

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	6.1%
Hypertension									
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	20.0%
Yang et al. 2012	United States (California, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, Rural Georgia, Kentucky, Louisiana, New Jersey)	Retrospective cohort	Colon	1999 - 2004	Patients recorded in cancer registry data (SEER)	Medicare claims from 12 months before to 3 months after cancer diagnosis	36,079	66+ years	76.0%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Primary hypertension Colon: 16.6% Rectal: 12.9%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	57.4%
Renal disease									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	Chronic renal failure: 2.4%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	1.6%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Chronic renal disease Colon: 4.6% Rectal: 3.5%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	4.1%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	Moderate or severe renal disease: 5.5%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	8.7%
Myocardial infarction									

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	2.6%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Colon: 5.8% Rectal: 4.7%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	3.0%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	2.6%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	6.3%
Chronic Obstructive Pulmonary Disease									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	20.9%
Frederiksen et al. 2009	Denmark	Retrospective cohort	Colorectal	2001-2004	Patients diagnosed with adenocarcinoma of the colon or rectum in Denmark	Hospital records and files of the Register of Medicinal Product Statistics, which contains information on the sales of pharmaceutical products in Denmark	8,763	Median age 69 years, interquartile range 61-76 years	11.0%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	Chronic pulmonary disease: 7.9%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Chronic pulmonary disease Colon: 6.3% Rectal: 5.7%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	Chronic pulmonary disease: 14.4%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	12.1%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	17.2%
Congestive Heart Failure									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	18.8%

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	3.7%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Colon: 5.8% Rectal: 3.3%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	4.5%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	10.8%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	14.5%
Peripheral Vascular Disease									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	6.7%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	1.7%
Sarfati et al. 2014	New Zealand	Retrospective cohort	Colon and rectal	July 2006 - June 2008	Patients recorded in cancer registry data	Hospital admissions up to 5 years before cancer diagnosis	Colon = 3,999 Rectal = 1,377	25+ years	Colon: 3.5% Rectal: 2.3%
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	3.8%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	5.3%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	11.7%
Rheumatological conditions									
Gross et al. 2006	United States	Retrospective cohort	Colorectal	1993 - 1999	Patients with stage 1 - 3 colorectal cancer, recorded in cancer registry data (SEER)	Medicare (inpatient, outpatient and physician) claims data from 2 years prior to 60 days after cancer diagnosis	29,733	67-99 years, mean 77.8 years	2.4%
Shack et al. 2010	North West of England, UK	Retrospective cohort	Colorectal	1997-2004	Patients recorded in cancer registry data	Hospital admissions 18 to 6 months prior to cancer diagnosis	29,563	15-99 years	0.8%

Condition	Location of study	Study type	Colon or colorectal cancer	Timeframe of cancer diagnosis	Study population	Source of information on comorbidity	N	Patient age	Prevalence reported
Pares-Badell et al. 2017	Hospital del Mar, Spain	Retrospective cohort	Colorectal	2000-2014	Patients recorded in cancer registry data	Hospital electronic health record - report closest to date of cancer diagnosis	2,670	Range not reported, mean 71 (+/- 12) years	0.6%
Mehta et al. 2018	Texas, United States	Retrospective cohort	Colorectal	2005 - 2011	Patients recorded in cancer registry data (SEER)	Medicare (inpatient and outpatient) claims data from 1 year to 30 days prior to cancer diagnosis	16,693	65+ years, mean 77.2 (+/- 7.3) years	Connective tissue disease / rheumatologic disease: 1.8%
Luque-Fernandez et al. 2020	Girona and Granada, Spain	Cross-sectional	Colorectal	2011	Patients recorded in cancer registry data	Spanish Primary Care Clinical database (conditions recorded within 6 months cancer diagnosis excluded)	1,061	24-97 years, mean 69.8 (+/- 12.7) years	9.8%

Appendix Table 2: The reported prevalence of thirteen health conditions in England or the United Kingdom

Condition	Reported prevalence	Population	Country	Year(s)	Data / Source	Obtained from
Liver Disease						
Liver disease	Only incidence information available: Age-standardised rate of hospital admissions due to liver disease: 131.2 per 100,000 persons	(England)	England	2016 - 2017	Hospital Episode Statistics (Office for National Statistics 2011 census, mid year population estimates)	PHE: "Liver Disease Profiles" (https://fingertips.phe.org.uk/profile/liver-disease/data#page/11/gid/8000063/pat/6/par/E12000004/ati/102/are/E06000015/iid/90892/age/1/sex/4)
Diabetes						
Type 1 or Type 2 Diabetes	5%	People aged 20-79 years (UK)	UK	2015	OECD Health at a Glance 2017 (Data obtained from International Diabetes Federation Atlas, prevalence estimate compiled for the UK from 4 unspecified data sources)	(https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2017/diabetes-prevalence_health_glance-2017-15-en)
Diabetes (type not specified)	6.8%	People aged 17+ years (England)	England	2017-18	Quality and Outcomes Framework	PHE: "CVD Profiles - January 2019" (https://fingertips.phe.org.uk/profile/cardiovascular/data#page/13/gid/1938133106/pat/15/par/E92000001/ati/153/are/E38000004/iid/219/age/1/sex/4)
Obesity						
Obesity	26%	People aged 16+ years (England)	England	2016	Health Survey for England	NHS Digital (https://files.digital.nhs.uk/publication/0/0/obes-phys-acti-diet-eng-2018-rep.pdf)
Obesity	24.0% men, 24.4% women	People aged 16+ years (England)	England	2004	Health Survey for England	Zaninotto et al (2009)
Dementia						
Dementia	4.3%	People aged 65+ years (England)	England	Six-monthly trends reported: Sept 2015 to Sept 2017	GP practice data / Quality and Outcomes Framework	PHE: "Recorded prevalence" using PHE Dementia Profile data tool (https://fingertips.phe.org.uk/profile-group/mental-health/profile/dementia/data#page/4/gid/1938133052/pat/6/par/E12000004/ati/102/are/E06000015/iid/91891/age/27/sex/4)
Dementia	Estimated 767,000 (95% uncertainty interval 735,000 to 797,000): (i.e. approximately 1.3% of this population)	(England and Wales)	England and Wales	2016	English Longitudinal Study of Ageing	Ahmadi-Abhari et al (2017)
Hemiplegia or Paraplegia						
No results found						

Condition	Reported prevalence	Population	Country	Year(s)	Data / Source	Obtained from
Cerebrovascular Disease (CVD)						
Stroke	1.90%	People aged 17+ years (England)	England	2017-2018	Quality and Outcomes Framework	PHE - "CVD Profiles - Stroke - May 2019" (https://fingertips.phe.org.uk/profile/cardiovascular/data#page/13/gid/1938133106/pat/46/par/E39000018/ati/153/are/E38000004/iid/219/age/1/sex/4)
Hypertension						
Hypertension	23.60%	People aged 16+ years (England)	England	2014	Quality and Outcomes Framework and Health Survey for England	National Cardivascular Intelligence Network, Public Health England (https://www.gov.uk/government/publications/hypertension-prevalence-estimates-for-local-populations)
Hypertension	13.90%	All ages (England)	England	2017/18	Quality and Outcomes Framework	PHE: (https://fingertips.phe.org.uk/profile/cardiovascular/data#page/3/gid/1938133106/pat/46/par/E39000018/ati/152/are/E38000004/iid/219/age/1/sex/4)
Renal Disease						
Chronic kidney disease	6.1% [95% credible intervals: 5.3, 7.0] (estimated)	People aged 16+ years (England)	England	2009-2011	Health Survey for England (HSE), 2011 Census, and 2011 Office for National Statistics (ONS) population estimates	Public Health England (https://www.gov.uk/government/publications/ckd-prevalence-estimates-for-local-and-regional-populations)
Moderate to severe chronic kidney disease	5.50%	(England and Wales)	England and Wales	April 2015 - June 2016	Clinical Practice Research Datalink	National CKD Audit (QMUL / LSHTM / UCL / Informatica)
Stages 3-5 chronic kidney disease	4.30%	People aged 18 + years (England)	England	2009-2010	Quality and Outcomes Framework	NHS publication: Chronic Kidney Disease in England: The Human and Financial Cost (https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf)
Chronic kidney disease	4.10%	People aged 18+ years (England)	England	2016 - 2017	Quality and Outcomes Framework	PHE: "CVD Profiles - Kidney disease - February 2018" (https://fingertips.phe.org.uk/profile/cardiovascular/data#page/13/gid/1938133109/pat/15/par/E92000001/ati/152/are/E38000004/iid/219/age/1/sex/4)
Myocardial Infarction (MI)						
MI / Heart attack	Only incidence information available: 198k heart attack hospital visits 2015-2017	(England)	UK	2015-17	Hospital Episode Statistics	British Heart Foundation (BHF) website (CVD Statistics - BHF UK Factsheet)

Condition	Reported prevalence	Population	Country	Year(s)	Data / Source	Obtained from
MI	Only event rate information available: (standardised to European standard population) Men: 154 per 100,000 population (95%CI 153 to 155) Women: 66 per 100,000 population (95%CI 65.3 to 66.7)	(England)	England	2010	Hospital Episode Statistics	Smolina et al (2012)
Chronic Obstructive Pulmonary Disease (COPD)						
COPD	2.57% (total population) 4.56% (people aged ≥35 years)	(England)	England	2016	Royal College of General Practitioners Research and Surveillance Network (RCGP RSC) database	Rayner et al (2017)
COPD	3.50%	People aged >15 years (England)	England	2001	Health Survey for England	Nacul et al (2011)
Congestive Heart Failure (CHF)						
CHF	1.40%	(UK)	UK	2014	Clinical Practice Research Datalink and Hospital Episode Statistics	Conrad et al (2018)
Heart failure	0.80%	People aged 17+ years (England)	England	2016-2017	Quality and Outcomes Framework	PHE - "CVD Profiles - Heart disease - February 2018" (https://fingertips.phe.org.uk/profile/cardiovascular/data#page/13/gid/1938133106/pat/46/par/E39000018/ati/153/are/E38000004/iid/219/age/1/sex/4)
Peripheral Vascular Disease						
Symptomatic peripheral arterial disease	3.4% (2000) and 2.4% (2014)	(UK)	UK	2000 and 2014	The Health Improvement Network database	Cea-Soriano et al (2018)
Peripheral arterial disease (PAD)	Estimated prevalence: 1.16%	Peaople aged 55-79 years (England)	England	2015	Whitehall II study	PHE: (https://fingertips.phe.org.uk/profile/prevalence/data#page/0/gid/1938133099/pat/6/par/E12000004/ati/101/are/E07000032)
Rheumatological Conditions						
Rheumatoid arthritis	0.70%	People aged 16+ years (England)	England	2017-18	Quality and Outcomes Framework	PHE: "Musculoskeletal diseases" (https://fingertips.phe.org.uk/profile/msk/data#page/0/gid/1938133186/pat/6/par/E12000004/ati/102/are/E06000015)
Systemic lupus erythematosus	97.04/100,000 person years (95% CI: 94.18 to 99.9)	(UK)	UK	1999-2012	Clinical Practice Research Datalink	Rees et al (2014)
Polymyalgia rheumatica	Point prevalence 0.87% (2011)	People aged 40+ years (UK)	UK	2011	Clinical Practice Research Datalink	Partington et al (2018)

Abbreviations: CKD - Chronic kidney disease; CVD - Cardiovascular disease; GP - General Practice; LSHTM - London School of Hygiene and Tropical Medicine; NHS - National Health Service; OECD - Organisation for Economic Co-operation and Development; PHE - Public Health England; QMUL - Queen Mary University London; UCL - University College London; UK - United Kingdom

Appendix Table 3: The crude and age-sex adjusted prevalence (%) of thirteen condition health conditions among patients diagnosed with colorectal cancer, lung cancer or Hodgkin Lymphoma in England between 2009-2013

	Cancer					
	Colorectal		Lung		Hodgkin Lymphoma	
Condition	***Crude***	**Adjusted (95% CI)**	***Crude***	**Adjusted (95% CI)**	***Crude***	**Adjusted (95% CI)**
Liver disease	*1.94*	1.84 (1.66, 2.02)	*2.26*	2.45 (2.12, 2.78)	*1.33*	1.34 (1.07, 1.61)
Diabetes	*10.64*	5.30 (5.08, 5.52)	*11.23*	5.40 (5.08, 5.72)	*5.71*	5.36 (4.83, 5.88)
Obesity	*2.49*	2.27 (2.07, 2.46)	*2.26*	2.27 (1.94, 2.59)	*2.41*	2.51 (2.13, 2.89)
Dementia	*1.89*	0.50 (0.47, 0.53)	*2.64*	0.69 (0.66, 0.71)	*0.43*	0.40 (0.26, 0.55)
Hemiplegia or paraplegia	*0.96*	0.50 (0.43, 0.58)	*1.60*	1.04 (0.85, 1.23)	*0.53*	0.51 (0.34, 0.68)
Cerebrovascular disease	*4.59*	1.58 (1.50, 1.66)	*7.58*	3.49 (3.20, 3.78)	*2.02*	1.83 (1.53, 2.13)
Hypertension	*38.98*	16.60 (16.30, 16.90)	*42.70*	18.69 (18.18, 19.19)	*16.01*	15.20 (14.31, 16.10)
Renal disease	*4.63*	1.53 (1.45, 1.62)	*6.02*	2.10 (1.91, 2.29)	*2.45*	2.24 (1.90, 2.57)
Myocardial infarction	*3.71*	1.26 (1.20, 1.32)	*5.86*	2.46 (2.28, 2.64)	*1.67*	1.49 (1.22, 1.76)
Chronic obstructive pulmonary disease	*13.20*	9.96 (9.54, 10.37)	*33.66*	24.59 (23.61, 25.58)	*10.34*	10.21 (9.47, 10.95)
Congestive heart failure	*4.52*	1.43 (1.36, 1.50)	*6.73*	2.55 (2.34, 2.75)	*1.79*	1.57 (1.30, 1.85)
Peripheral vascular disease	*3.48*	1.17 (1.10, 1.24)	*7.99*	2.97 (2.79, 3.15)	*1.47*	1.30 (1.05, 1.55)
Rheumatological conditions	*2.01*	1.00 (0.90, 1.09)	*3.49*	2.11 (1.86, 2.35)	*2.32*	2.40 (2.03, 2.76)

Abbreviations: CI - confidence interval

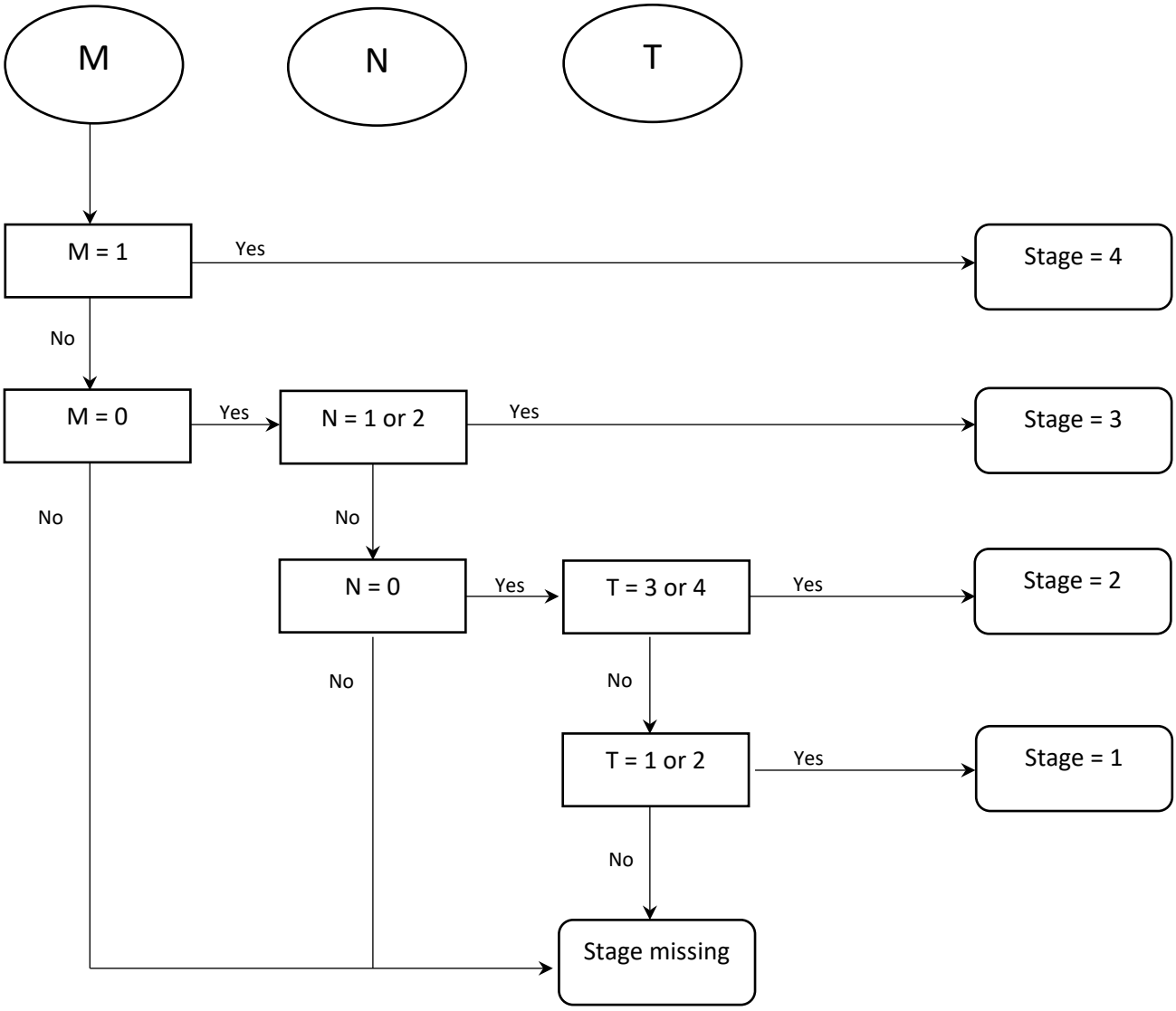
Appendix Table 4 - Performance Status Scales (the Zubrod Scale and the Karnofsky Scale)

Two commonly used Performance Status scales are the Zubrod Scale and the Karnofsky scale.

Zubrod Scale		**Karnofsky Scale**	
0	Normal activity	**100**	Normal; no evidence of disease
		90	Able to perform normal activities with only minor symptoms
1	Symptomatic and ambulatory; cares for self	**80**	Normal activity with effort; some symptoms
		70	Able to care for self but unable to do normal activities
2	Ambulatory >50% of time; occasional assistance	**60**	Requires occasional assistance; cares for most needs
3	Ambulatory ≤50% of time; nursing care needed	**50**	Requires considerable assistance
		40	Disabled; requires special assistance
		30	Severely disabled
4	Bedridden	**20**	Very sick; requires active supportive treatment
		10	Moribund

Source: West and Jin (2015), JAMA Oncology

Appendix Figure 1: Flow diagram to show the process followed by the stage algorithm to derive the overall grouped TNM stage at diagnosis variable, based upon individual components of tumour (T), nodes (N) and metastases (M)



Source: Benitez-Majano et al. (2016) British Journal of Cancer

Appendix A: The domains of the England Indices of Multiple Deprivation (IMD) 2010

The seven domains of the England IMD 2010 (and their respective weights)[80]:

- Income Deprivation (22.5%)
- Employment Deprivation (22.5%)
- Health Deprivation and Disability (13.5%)
- Education, Skills and Training Deprivation (13.5%)
- Barriers to Housing and Services (9.3%)
- Crime (9.3%)
- Living Environment Deprivation (9.3%)

Appendix B: Presentations at national and international conferences

The findings of the work undertaken for this thesis have been presented at the following conferences.

Oral presentations at conferences

- Fowler H, Belot A, Ellis L, Maringe C, Luque-Fernandez MA, Njagi EN, Navani N, Sarfati D, Rachet B. *Socio-economic position and comorbidity prevalence in cancer patients – a population-based study*. North American Association of Central Cancer Registries & International Association of Cancer Registries combined conference, Vancouver, Canada (June 2019)
- Fowler H, Belot A, Njagi EN, Luque-Fernandez MA, Maringe C, Quaresma M, Kajiwara M, Rachet B. *Persistent inequalities in ninety-day colon cancer mortality*. Public Health England Cancer Data and Outcomes conference, Manchester, United Kingdom (June 2017)

Poster presentations at conferences

- Fowler H, Maringe C, Rachet B, Luque-Fernandez MA. *Use of administrative data to assess comorbidities in cancer patients: validity and prevalence*. Public Health England Cancer Data and Outcomes conference, Manchester, United Kingdom (June 2017)